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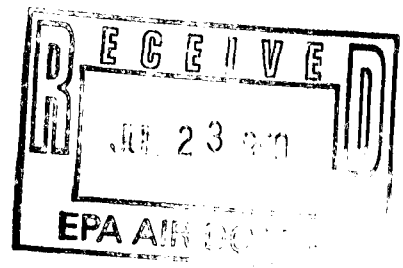
Chemetals Incorporated
711 Pittman Road
Baltimore, Maryland 21226
301-789-8800

Dr Denis F. DeCraene
Director-Business Development

A-90-16
IV-D-56

CHEMETALS



July 23, 1990

Public Docket A-90-16
Air Docket (LE-131)
Room M-1500
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, D.C. 20460

RE: Comment on the request of Ethyl Corporation Dated May 9, 1990 for a Fuel Additive Waiver Clean Air Act Section 211(f)(4)

Dear Sir/Madam:

Chemetals has submitted comments on the waiver request of Ethyl Corporation for the use of HiTEC 3000, a manganese-containing additive in unleaded gasoline in the United States.

In connection with our own comments, Chemetals has retained the services of Dr. Albert Kolbye of Kolbye Associates to examine the scientific literature and offer a professional toxicologist's opinion on the health issues relating to the use of HiTEC 3000 in unleaded gasoline in the United States.

Attached please find the statement of Dr. Kolbye for inclusion in the docket. Also attached please find a compendium of the literature analyzed by Dr. Kolbye and arriving at his conclusion that the use of HiTEC 3000 does not represent a health hazard.

Very truly yours,

Denis F. DeCraene

Dr. Denis F. DeCraene
Director-Business Development

enclosures

cc: Mary T. Smith
Director-Field Operations
and Support Division
(EN-397F)

DFD:mrt

KOLBYE ASSOCIATES
EVALUATION OF PROPOSED USE OF MMT

Kolbye Associates
7313 Helmsdale Road
Bethesda, MD 20817
July 20, 1990

INTRODUCTION:

This is a brief report of our scientific analysis and evaluation of the proposed use of HiTech 3000 as a manganese additive to gasoline.

We have conducted an extensive search of recently published scientific literature and critically evaluated these reports in conjunction with previous knowledge of the potential toxicity of various manganese-containing compounds.

OUR OPINION IN SUMMARY

We have no objection to the proposed use of MMT nor do we believe that any significant health problems will result from its use in this manner. In addition, future scientific research will continue to develop additional knowledge about traces of environmental manganese in various media such as ambient air. Any potentional hazard can be monitored continuously without any risk to public health. We see no reason whatsoever to deny the waiver for MMT.

1) MANGANESE IS ESSENTIAL TO HUMAN HEALTH.

There can be no question of the nutritional importance of manganese in the diet. Manganese is an essential co-factor and component of many enzymes, notably in the mitochondria. Deficiencies are well recognized in laboratory animals. In humans there is corresponding evidence but to a lesser degree of documentation. Obviously, the human body, through biological evolution, requires manganese and is experienced in metabolizing manganese compounds ingested in the diet. Variations of absorption and excretion exist, when infants, pregnant women, and older adults are compared. However, the only human disease problems attributed to manganese were caused by occupational inhalation exposures for protracted time-periods to high concentrations of manganese oxides (at levels of tens of milligrams per cubic meter of air).

2) MANGANESE DOES NOT POSE A PUBLIC HEALTH RISK AT AMBIENT LEVELS.

Manganese is the 12th most common element of the earth's crust. Airborne dust from ground soil is a major source of pulmonary exposure for humans, as is inhalation of air near ocean spray. There are many data on airborne levels of manganese compounds. In a recent Canadian report (1988),

urban levels were reported on the average to range from 65 nanograms per cubic meter to 166. In similar fashion both fresh water and salt water contain appreciable levels of manganese ranging from low to high micrograms per liter. Appreciable levels of manganese compounds occur in many foods notably certain grains and vegetables. It is estimated that humans ingest, on the average, between 4 and 9 milligrams of manganese per day in their diets. We can see that the most substantial sources of human exposure to manganese are dietary and far greater than those usually involved with inhalation. It is true that manganese, when inhaled and absorbed into the blood stream, can follow different pathways of distribution in the body. Most, however, will go to the liver within a short time and be metabolized and excreted. Some may directly enter the brain and here there is evidence of a longer biological half-life. However, the question of neurotoxicity clearly depends on dose. There is strong evidence that only very high concentrations of manganese in inhaled air for protracted periods of time are potentially toxic to brain cells. The ambient air exposures to manganese arising from the proposed use of MMT are infinitesimal by comparison and cannot by any justification from all presently available evidence, be used as a basis to prohibit the usage of MMT.

3) MANGANESE IS EXCRETED FROM THE HUMAN BODY.

Dietary manganese is poorly absorbed, usually 4 percent at most. Inhaled manganese may be absorbed to a greater extent through the alveolar membrane, provided that prerequisite conditions are fulfilled. When high concentrations are involved in inhaled air, occupational diseases have been observed. The same diseases have never been observed in relation to low concentrations of manganese in inhaled air. Low concentrations of manganese of inhaled air contribute very little to the body burden of manganese in most human beings. Homeostatic mechanisms exist in the body to facilitate and regulate manganese excretion. These mechanisms are not disturbed by the very slight airborne exposures that might occur from time to time.

4) MANGANESE IS NOT A KNOWN CARCINOGEN.

Various relatively short-term tests have been performed on a range of manganese compounds with no alarming results. It is noteworthy that after two year exposures of monkeys to inhaled manganese oxide, no precancerous or cancer lesions were reported by the authors (Bird). In passing, it should be noted that any compound given at toxic doses to laboratory animals has a greater likelihood of facilitating the

expression of spontaneously arising cancers. The available epidemiological evidence from miners and factory workers does not raise any suspicion of an increased risk for cancer.

5) MANGANESE IS ONLY NEUROTOXIC TO HUMANS AT HIGH MILLIGRAM INHALATION EXPOSURE LEVELS.

As indicated earlier in this document, only at very high and prolonged inhalation exposures (tens of milligrams per cubic meter of air) has there been documented epidemiological evidence of human disease. Two manifestations occur, one being neurotoxicity resembling Parkinsonism and the other being pneumonitis. These air concentrations involved are many orders of magnitude higher than those anticipated by worst case estimates of additional inhalation exposures caused by use of MMT.

6) OCCUPATIONAL SAFETY INHALATION STANDARDS ARE ORDERS OF MAGNITUDE GREATER THAN PRESENT OR EXPECTED AMBIENT AIR LEVELS.

The present TWA limits recommended by ACGIH and set as a ceiling limit by OSHA for manganese oxide compounds and dust in air in a work setting for an 8 hour day are 5 milligrams per cubic meter. There is no evidence that prolonged and

repetitive inhalation exposures of humans to this concentration of manganese oxides in air has caused any demonstrable recognized health problem. This judgement was arrived at by many scientists acting independently and jointly on various committees, after extensive evaluations of all available scientific evidence concerning occupational hazards to inhaled manganese oxides.

7) THE TOXICITY OF MANGANESE IS DIFFERENT FROM AND NOT RELATED TO THE TOXICITY OF LEAD.

Clearly, lead compounds have no known useful biological functions and have been reported by many epidemiologists and biomedical scientists to cause a spectrum of adverse health effects even at relatively low levels of human exposure. Two major sources of excessive exposure to lead exist: 1) the ingestion of lead-containing paint, and 2) lead in certain foods which previously occurred at very substantial levels especially in certain canned foods. Lead toxicity is determined by the unique characteristics of each particular compound of lead. The same is true for each and every chemical compound in the world. Certain lead salts are absorbed, slowly excreted and can cause brain and kidney damage. While the body has certain mechanisms to detoxify and

excrete lead, they are not remarkably efficient. This is probably because lead is not an essential element for body function; to the contrary, it is a very effective biological poison.

Manganese, only when inhaled in excessive amounts, causes a much more specific pattern of neurotoxic damage. This probably reflects overload beyond normal capabilities of cells to use manganese constructively. There are indications that the trivalent form of manganese is a powerful oxidant, whereas the normal function of divalent manganese is as an antioxidant. One cannot say that there is a biologically required or normal level of lead in the body. One can say that manganese is required for normal body function and only becomes toxic to brain when excessive amounts are inhaled over prolonged periods of time.

8) THE USE OF HAIR SAMPLING TECHNIQUES TO ESTIMATE HUMAN EXPOSURE TO MANGANESE HAS NOT BEEN VALIDATED.

Among experienced scientists, there is concern about the accuracy with which residues of various compounds are measured in hair and whether or not they truly reflect the past pattern of human exposure. This is because direct exposure of hair to a variety of compounds contained in air or in various

cosmetics and shampoos may confound interpretation. This is particularly true with regard to manganese because of its common occurrence in airborne dust which is deposited on body surfaces, including hair. Validation studies on this topic have been inadequate. More importantly, there are data to indicate that such findings misrepresent the body burden of manganese in humans. Quantitative analyses of 24-hour urine excretion or blood levels are likely to be more accurate, although these need further validation also.

9) WHILE DEFICIENCIES Of DIETARY INTAKES OF IRON AND CALCIUM INCREASE MANGANESE ABSORPTION, THEY ARE NOT DIRECTLY RELEVANT TO THE ISSUE INVOLVED HERE.

Many factors influence the absorption through the gastrointestinal tract of dietary components such as divalent cations. These include among others, manganese, iron, and calcium. Some exist in different states of valency. Other dietary components such as ascorbic acid also influence absorption. Iron-deficient humans or those with a propensity to absorb higher amounts of iron such as pregnant women, infants, and people with hemochromatosis will absorb higher amounts of iron than normal. By analogy, they are likely to absorb higher amounts of manganese in the diet if under

similar circumstances. These observations are largely irrelevant to the present issue involving MMT, because inhalation exposure to manganese follows different characteristics, if in fact, the inhaled manganese is absorbed through the alveolar membrane into the blood stream. It is to be expected that a significant portion of inhaled manganese will be adsorbed on other particulates and expelled by ciliary action back to the oropharynx and swallowed where it then is treated by the body as dietary manganese. As such, very little will be absorbed through the gastrointestinal tract under any set of conditions. Persons with higher than normal absorption may absorb relatively higher amounts of manganese than do most people, but most likely it will be readily excreted from the body. We see no problem in this regard as far as the proposed use of MMT is concerned.

CONCLUSIONS

Manganese is required in the diet as an essential nutrient for human health. It is usually readily excreted from the human body. It is not a known carcinogen. Its toxicity is unrelated to lead. Only when humans are exposed by inhalation for prolonged periods of time to air concentrations in the tens of milligrams per cubic meter of air, has disease occurred. Manganese does not pose a public

health risk at ambient concentrations in air, which in turn will not be significantly increased at all by the proposed use of MMT. Occupational safety standards permit orders of magnitude greater exposures to inhaled manganese than could ever under any circumstances be expected from the proposed use of MMT.

BIBLIOGRAPHIC REFERENCES

This report has been prepared after an extensive review of the worldwide literature on manganese, including both scientific publications and governmental commissioned reports. The scientific literature concerning nutritional aspect of manganese has been extensively reviewed, as has all available information on manganese toxicity.

The latter include review of EPA's Health Assessment Document, the Canadian Report, various publications by Davis, Donaldson, Gottschalk, Silbergeld, and many other reports. This database is too extensive for us fully document at this time, but any reader requiring further information as to sources is asked to telephone area code 301/320-2900.

CURRICULUM VITAE

ALBERT CHRISTIAN KOLBYE, JR., M.D., M.P.H., J.D.
7313 Helmsdale Road
Bethesda, Maryland 20817
(301) 320-2900

EDUCATION:

William Penn Charter School Philadelphia, Pennsylvania	H.S.	1953
Harvard College Cambridge, Massachusetts (Pre-Med, Pre-Law and Geology)	A.B.	1957
Temple University School of Medicine Philadelphia, Pennsylvania	M.D.	1961
University Hospitals Madison, Wisconsin (Internship - Mixed Medicine)		1962
School of Hygiene and Public Health The Johns Hopkins University Baltimore, Maryland	M.P.H.	1965
The School of Law University of Maryland Baltimore, Maryland	J.D.	1966
Federal Executive Institute Charlottesville, Virginia		1974

LICENSURES:

To Practice Medicine - State of Maryland since 1962
To Practice Law - Maryland and District of Columbia since 1967
Board Certification in Preventive Medicine and Public Health

PROFESSIONAL BACKGROUND:

Internship, University of Wisconsin, Madison - 1962
Residency, Maryland State Department of Health - 1964
United States Public Health Service, Commissioned Corps - 1962-1982:

Heart Disease Control Program - 1962-1966
Staff Director, Smoking & Health Program - 1967-1968
Staff Director, Secretary's Commission on Pesticides - 1969
Deputy Director, Bureau of Foods, FDA - 1970-1972
Associate Bureau Director for Toxicological Sciences, Bureau of Foods, FDA - 1972-1982
Assistant Surgeon General (07) USPHS - 1971-1982
President - The Nutrition Foundation, Inc. 1982-1984
Director - Kolbye Associates 1984 to Present
Past President - International Society of Regulatory Toxicology & Pharmacology 1987-1988

FELLOWSHIPS AND MEMBERSHIPS:

Fellow of:
American Academy of Clinical Toxicology
American Public Health Association
American College of Legal Medicine
American College of Preventive Medicine
International Academy of Environmental Safety

Co-Editor:
Regulatory Toxicology and Pharmacology
Academic Press

Member of:
American Medical Association
American Bar Association
Maryland State Bar Association
Maryland Medical Chirurgical Society
Society of Toxicology
Environmental Mutagen Society
Society for Epidemiologic Research
Society of Ecotoxicology and Environmental Safety
New York Academy of Sciences
Toxicology Forum
Society for Preventive Oncology
International Commission for Protection Against Environmental Mutagens and Carcinogens

CHAIRMANSHIPS OR
STAFF DIRECTORSHIPS:

The Surgeon General's Reports to Congress on the Consequences of Smoking - 1967, 1968 and 1969
The Secretary's Commission on Pesticides and Their Relationship to Environmental Health, DHEW - 1969
Secretary's Representative to the Interagency Pesticide Agreement - 1970

The Health Hazards of Mercury, DHEW - 1971

Health Hazards Evaluation Board, Bureau of Foods, Food and Drug Administration - 1972-1982

Research in Human Subjects, FDA - 1972-1982

Interagency Epidemiological Working Group on Saccharin - 1976-1980

Interagency Working Group on Mechanically Deboned Meat, U.S. Department of Agriculture - 1976-1977

WHO Scientific Consultant for Preparation of Environmental Health Criteria for Nitrates, Nitrites, and N-Nitroso Compounds, Environmental Health Criteria 5, WHO Geneva - 1977

FD&C Red No. 40 Working Group - 1976-1981

Subcommittee 4 (Regulatory and Legislative) International Commission for Protection Against Environmental Mutagens and Carcinogens - 1978-1982

Interagency Working Group on Saccharin Epidemiology

Interagency Working Group on Nitrite Research

RECENT POSITIONS HELD:

Rear Admiral, USPHS - 1971-1982
(Assistant Surgeon General)

Deputy Director, Bureau of Foods, FDA - 1970-1972

Associate Bureau Director for Toxicological Sciences, Bureau of Foods, FDA - 1972-1982

President, The Nutrition Foundation, Inc.
Washington, DC - 1982-1984

PRESENTATIONS AND PUBLICATIONS:

Over 100 invited speeches and published papers concerning the safety of chemicals and foods, animals and human nutrition, and public policy issues and law.

(Detailed bibliography to be provided upon request.)

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BIBLIOGRAPHIC REFERENCES

This report has been prepared after an extensive review of the worldwide literature on manganese, including both scientific publications and governmental commissioned reports. Recent sources are represented by the attached print-out from one of our computerized searches of the literature. The scientific literature concerning nutritional aspect of manganese has been extensively reviewed, as has all available information on manganese toxicity.

The latter include review of EPA's Health Assessment Document, the Canadian Report, various publications by Davis, Donaldson, Gottschalk, Silbergeld, and many other reports. This database is too extensive for us fully document at this time, but any reader requiring further information as to sources is asked to telephone area code 301/320-2900.

The following represents brief summaries of recent publications of direct relevance to the MMT issue.

EPA 1984 Report

A comprehensive report was prepared by EPA entitled Health Assessment Document for Manganese was published in 1984. This report documents quite well that manganese occurs in many media on a widespread basis, in air, water, food and soil.

We have extensively reviewed this report and do not disagree with many descriptive reviews of exposure to, ingestion of, or inhalation of manganese, and potential parameters of absorption, metabolism and excretion of various manganese containing compounds. However, we do disagree with some of the conclusions and implications presented in this EPA report. There is little question that exposure to toxic levels of manganese compounds over a protracted period of time creates the potential for toxicity notably in CNS and to some extent the respiratory tract. Nor do we share any substantive concern that the very minor additional anticipated human exposures to manganese oxides have any causative relevance with regard to the induction of cancer. We see no evidence of any problem in this regard.

KOLBYE ASSOCIATES
7313 HELMSDALE ROAD
BETHESDA, MARYLAND 20817

A) AIBR/SCHAUSS HAIR DATA

This document contains a variety of data from hair analyses that Kolbye Associates do not consider to be reliable indicators of exposure and absorption into the body. One reason for this is that manganese occurs airborne as dust particulates and thus topical exposure to hair can confuse the alleged significance of the findings. We believe that blood levels more accurately reflect body status. We do not believe that the biological correlation of findings in hair as compared to other parameters has been validated.

B) ABBOTT PAPER - 1987

Abbott mentions that the expected increase in airborne manganese concentration would be 0.02 micrograms per cubic meter. Average urban air concentrations in U.S. are reported to be 0.03 micrograms per cubic meter. (U.S. EPA 1984) Abbott mentions that the actual intake under rather extreme conditions, assuming all inhaled manganese oxides were absorbed would be only 10 micrograms per day. The WHO 1973 have estimated that adults ingest at least 2 or 3 milligrams per day of manganese in their diet with usually less than 5 percent absorbed by the gastrointestinal tract. (WHO 1981) Abbott also makes several very good points in differentiating the potential consequences of exposure to manganese as compared to lead.

When manganese is present in air at levels approximating or exceeding 5 milligrams per cubic meter over a protracted period of time irritation to the pulmonary tract can occur.

Abbott also discusses the CNS effects of manganese and talks about two stages, the first representing psychological disturbances which may be reversible and the second more advanced stage of a definite syndrome which ultimately can resemble Parkinson's syndrome. While impairment of dopamine appears to be the mechanism, it appears to be induced only at levels one thousand to ten thousand times higher air concentrations than those likely to occur as a result of using MMT in automotive gasoline. Abbott cites the 1981 WHO report as finding no increases in lung tumors occurring in individuals occupationally exposed to substantial levels of manganese. Abbott also cites a paper by Stenback and Rowland (1979) indicating that hamsters were not at increased risk of lung tumors after installation of 1.5 milligrams per week for 20 weeks with or without benzo(ad)pyrene.

As far reproductive effects are concerned, Abbott provides evidence that they occur only at very high exposure levels thousands of times higher than those anticipated with the use of MMT.

C) CALIFORNIA SENATE BILL 107

This Bill proposes hair analysis on prisoners.

E) DEICHMANN - TOXICOLOGY & OCCUPATION - Conn et al (Human Sweat)

This article documents the fact that manganese can be excreted in human body sweat at concentrations of 17 micrograms per liter or higher.

F) GOODHART & SHILS - M. NUTRITION 1980

This article documents that absorbed manganese is excreted largely in the intestinal tract either in bile or pancreatic juice. It also reports the average daily intake of manganese to be be between 3 and 9 milligrams with about 40 percent being absorbed. An extensive description is presented showing the importance of manganese as a nutrient in activating a large number of metal-enzyme complexes important to normal body function and growth.

G) INDUSTRIAL TOXICOLOGY - 1949

Somewhat outdated reference containing use in toxicity information.

H) ARENA: POISONING

Short comment concerning treatment with chelating agents or anti-Parkinsonian drugs.

I) PROCTER ET AL CHEMICAL HAZARD - WORKPLACE

This article reviews various data emphasizing that very high exposure levels can cause human toxicity ranging from approximately 6.8 up to 42 milligrams per cubic meter in the workplace environment.

J) NTP - 1989 RESEARCH

Nutritional and pharmacokinetic/metabolic studies are currently underway by the Center for Food Safety and Applied

Nutrition of the FDA in conjunction with the National Toxicology Program.

M) LETTER TO HODGES

This letter was written by Rebello and Gottschalk presents the thesis that hair manganese levels may predict violent behavior. We do not deem these data to be reliable and note that higher levels of lead were also found in the hair samples from some prisoners.

N) MAUGH IN SCIENCE ABOUT HAIR

Another paper that seems more concerned with below normal concentrations of manganese in hair in association with below normal mental performance.

O) RALL - NIEHS - 1990

Dr. David Rall makes certain statements and raises certain questions. His points: 1) No disagreement, but there are important differences from lead. 2) Skin absorption of MMT is not relevant unless people are washing their hands in gasoline and nasal-brain "straight shot" is highly speculative and unproven. 3) This statement is erroneous in that early stages of CNS damage can be arrested by cessation of exposure and can be treated with chelating agents and anti-Parkisonian drugs. 4) Apparently most of the manganese not exhausted through the tailpipe remains in the exhanust system and thus Dr. Rall's comments are inappropriate. 5) Contains inappropriate implications and comparisons to lead toxicity. 6) He implies a lack of data directly applicable to the health of humans exposed to auto exhaust from cars using MMT-containing gasoline. This is a syllogisn in that you can't have a chicken before you have an egg. The Canadians apparently have used MMT in gasoline without any noticable adverse effects on human health. Dr. Rall's comment speculates on safety without any foundation in fact. 7) Dr. Rall comments that "Manganese may act via the same mechanisms as other heavy metals (especially lead). Synergism is possible and has not been studies for any organ system. Dr. Routt Reigart (University of South Carolina Medical School) raised the issue especially with respect to the CNS." This comment is not founded on fact and to our way of thinking reflects a substantial amount of ignorance about the biochemistry and essentiality of manganese as a nutrient. As far as speculating on modes of manganese potential neurotoxic effects we consider his comment both inappropriate and ill-informed.

Q) NEEDLEMAN SUBMISSION - 1990

Dr. Needleman's calculations about estimated environmental loading of manganese resulting from MMT usage in gasoline is erroneous, ill-informed and unreasonably speculative. It also contains ad personam comments against Ethyl Corporation that is inappropriate.

S) DYNAMAC REPORT - 1986

This extensive report on MMT after review by us appears to be accurate and comprehensive with respect to the information presented.

T) HiTEC-3000 AUTO EXHAUST

This report contains particulate emission data.

U) DAVIS ET AL - JAPCA

The data contained in this article emphasize that the primary source of airborne manganese derives from the earth's crust and that only in certain California locations is the contribution from automotive sources appreciable mainly, in Southern California. There is not clear proof that the contribution attributed to the usage of motor vehicles is in fact accurate. This paper has a methodology problem.

V) SMYTH ET AL - J OCCUP MED

This paper is essentially derived from case studies of employees in the ferromanganese industry and presents data dealing with exposures to dust and fumes.

W) DONALDSON ET AL - MANGANESE

These authors present data on the autoxidation of dopamine by metal ions including manganese. Free radicals are formed. This mechanism is suggested to account for manganese neurotoxicity.

X) MANGANESE CENTRE - MAY 1989 REPORT

This report explains many confounding factors related to the health of Aborigines in Groote Eylandt. Swedish data are also discussed as are Belgium data and Canadian data.

J-1) MANGANESE & ENVIRONMENTAL AND OCCUPATIONAL HEALTH PROBLEMS - HART - 1989

The author discusses various TLVs and presents summaries of various studies from around the world.

Y) MERCK INDEX - 1983

Various forms of manganese.

Z) RDA - 1989

Average dietary intake of manganese is slightly over 2 milligrams per day with only 2-3 percent contributed by drinking water. Dietary requirements are known to exist but have not been defined.

AA) COTZIAS - J. NEUROTOXICOLOGY

This author recognizes that manganese neurotoxicity can simulate Parkisonism. However, the author does not believe that manganese is a major cause of Parkison's disease. An extensive presentation is made concerning manganese in relation to catecholamines and extrapyramidal disease.

BB) ROELS, H ET AL - AJIN

One hundred and forty-one male workers exposed on the average of 7.1 years to airborne manganese dust at about 1 milligram per cubic meter were studied. Questions were raised concerning preclinical intoxication.

CC) APPENDIX 8-HiTEC-3000

An extensive presentation of manganese in diet and in air which also estimates an additional 0.4 micrograms additional daily exposure from MMT use.

DD) MANGANESE CENTRE - DECEMBER 1988

Updated review on manganese.

GG) EPA AIR DOCKET/EDF

Dr. Silbergeld objects to the approval of MMT alleging that manganese will accumulate in the body and cause neurotoxicity somewhat similar to problems known to be associated with lead.

She stated the obvious that high level exposures to manganese over protracted periods of time are associated with neurotoxicity and also stating that there is much information we do not know.

JJ) FASEB REPORT

A 1979 review by FASEB prepared under contract to the FDA presented an evaluation of manganous salts in food ingredients in relation to potential consequences to human health. It describes the essentiality of manganese as a nutrient and the relatively low oral toxicity due to restricted absorption and deficient excretion. It does contains a reservation about the lack of information concerning the use of manganous oxide as an intentionally added ingredient in food.

QQ) TRACE ELEMENTS - NUTRITION FOUNDATION 1976 (VOL. 2)

An extensive presentation is made of the importance of manganese to mitochrondial function, especially with regard to enzyemes concerned with carbohydrate metobolism.

SS) CASARETT & DOULL'S TOXICOLOGY - 3RD EDITION 1986

This article points out that the biologic half life in the body generally is 37 days, but longer in the brain. Manganese readily crosses the blood brain barrier. It also states chelating agents do not produce remarkable recovery. L-dopa seems to work better. On page 811 a suggestion is made that manganese among other compounds can potentiate the response to sulfur dioxide. It also emphasizes on page 350 that manganese induced pneumonia is often fatal. On page 583 typical manganese concentration in air is reported at 0.1 micrograms per cubis meter, and 60 micrograms per liter in surface water. On page 775 manganese gluconate and oxide are reported as food additives.

TT) NUTRITION & DRUG INTERACTIONS - 1978

A case report that administration of alfalfa tea containing high levels of manganese helped to control juvenile diabetes.

UU) TOXIC SUBSTANCES & HUMAN RISK - TARDIFF & RODRICKS 1987

The earlier TLV for air was 6.0 milligrams per cubic meter. By extrapolation the authors conclude that 15.0 ppm manganese in water would be acceptable.

L) EPA JUNE 22, 1990 - WAIVER HEARING

EPA's panel heard the testimony of a variety of persons. Dr. Silbergeld testified that manganese was another lead, but could not support her contention except by speculations that were not supported by factual scientific evidence. Dr. Donaldson gave a somewhat similar style of presentation directed towards his belief that manganese levels in hair when elevated are associated with violent human behavior. Again, upon critical review in our opinion his testimony is unfounded. The best questions were asked by Mr. Poirier who elicited the response from Dr. Ter Haar that the manganese in automotive exhaust was in the tetraoxide form and represented and infintestimal amount as compared either to the amount of manganese in the MMT added to gasoline or the amount of manganese in airborne dust originating from ground-dust from the earth's crust.

VV) CASARETT & DOULL'S TOXICOLOGY - 2ND ED - 1980

Comprehensive information dealing with manganese toxicity is available in this textbook which is one of the premier textbooks in toxicology. On page 450 reference is made to two experiments of interest to the instant problem. Neff et al 1969 involved I.P. administeration to squirrel monkeys which then resulted in substantial decreases of brain dopamine and serotonin. One hundred day exposure of rats by inhalation to manganese dioxide at concentrations of 47 mg manganese per cubic meter for 5 hours a day, 5 days a week produced no behavior or histologic adverse effects (Martone 1964).
On page 705 references made in table 28-1 that a tentative biologic TLV for manganese in urine would be 50 mg per liter. In table 17-1 on page 410, the human body burden for a 70 kilogram person of manganese is estimated at 20. Also noted in this table is an estimated daily intake of 5 milligrams per day and that the average concentration of manganese in the earth's crust is 1,000 parts per million which translates to one part per thousand. In table 17-2 referring to drinking water on page 411, the desirable upper limit for manganese in water was cited at 0.05 milligrams per liter. The highest levels found approximated 1.32 mg per liter. In table 17-3 on page 411, referring to air concentrations in the United States the average concentration of manganese in air was 0.10 micrograms per cubic liter with a maximum found of 9.98 micrograms per cubic liter. Table 9-2 on page 191 illustrates substantial differences in how manganese at high doses can damage certain anatomical areas of the brain that differ substantially from the deposition pattern of lead. In table

12-2 on page 267 reference is made to manganese induced pneumonia. In table 17-4 the occupational exposure limit for manganese as a TWA was 5 mg per day. In table 23-1 five forms of manganese are noted as approved food additives: chloride, gluconate, glycerophosphate, oxide and sulfate. On page 220 reference is made to the work of Klaassen and Plaa respectively about manganese loading rats and the cholestatic effects.

WW) NUTRITIONAL TOXICOLOGY VOL 1 - 1982

An interesting aspect of manganese physiology is referred to herein on page 144 suggesting that manganese may have a protective affect against experimental atherscleros is.

XX) NUTRITION REVIEWS - PRESENT KNOWLEDGE IN NUTRITION - NF 1984

An extensive discussion on manganese is presented with emphasis on the various dietary factors influencing its uptake from the gut (page 559). Additional information about the enzymatic functions and effects manganese deficiency are presented. Mutant gene mice and mink apparently have unusual susceptibilty to manganese deficiency. The latter is associated with impairment glucose tolerance curves in mammals. Manganese deficient animals have a propensity to convulse. Reference is made (sub-reference 52 that the L-dopa treatment of Parkinsonism seems to involve changes in manganese metabolism (page 565). Nutritional requirements for humans are discussed here also. On page 566 the author state that there is a wide margin of safety before inhalation toxicity to manganese is induced.

EE) ASTRUP REFERENCES - 1990

This is a literature survey published the International Manganese Institute in Paris. One reference by Kondakis et al presents data that Greeks exposed to high levels of manganese in drinking water had elevated hair manganese levels and damage to their CNS. Stauber and Florence report that airborne manganese dust can be trapped in hair and incorporated therein. Vescovi et al discuss manganese neurotoxicity in relation to catecholamine autoxidation. Elias et al report chromosomal aberrations in blood lymphocytes of welders exposed to manganese. Bleecker presents as a final common pathway for Parkinsonism several compounds including manganese. Raghupathy et al emphasize

problems associated with external contamination of hair by metals. Reference is made to an NTIS data base dated 1988.

L-1) BARBEAU - MANGANESE AND EXTRAPYRAMIDAL DISORDERS (RE: COTZIAS 1984)

An extensive review emphasizing the importance of neuromelanin, deemphasizing autoxidation of catecholamines.

M-1) TANG - BIOGRAPHY OF DR. GEORGE C. COTZIAS - 1984

Review and tribute to Dr. Cotzias.

N-1) DONALDSON - MANGANESE IN PHYSIOLOGICAL AND BIOCHEMICAL PROCESSES - 1984

Overview introduction to special issue of neurotoxicology.

O-1) LAI ET AL, NEUROTOXIC EFFECTS OF MANGANESE - 1982

Suggest that at subtoxic levels manganese may prevent brain damage caused by aging.

P-1) MARKESBERY ET AL - BRAIN MANGANESE CONCENTRATIONS IN HUMAN AGING AND ALZHEIMER'S DISEASE - 1984

The brains of patients with Alzeimer's disease were examined for manganese content and no significant difference was found between patients and controls.

Q-1) COHEN - OXY-RADICAL TOXICITY IN CATECHOLAMINE NEURONS - 1984

Oxygen radicals and peroxides are implicated in causing damage to catecholamine neurons.

R-1) SETH AND CHANDRA - NEUROTRANSMITTERS IN RATS DURING MANGANESE POISONING - 1984

Neonatal exposure of mice and rats to manganese is associated with tissue accumulation and neurotoxicity.

S-1) LOWN ET AL - MATERNAL (MOUSE) INHALATION EXPOSURE TO MANGANESE AFFECTS - 1984

Pregnant mice were exposed by inhalation to MnO_2 dust and various findings were reported.

T-1) HALLIWELL - MANGANESE IONS, OXIDATION REACTIONS AND THE SUPEROXIDE RADICALS - 1984

Mn2+ stimulates oxidative degeneration of dopamine and adrenalin,

U-1) DONALDSON AND LA BELLA - EFFECTS OF MANGANESE ON CHOLINERGIC RECEPTOR - 1984

Free radicals or cytotoxic quinones apparently arise from dopamine autoxidation caused by manganese.

V-1) HURLEY ET AL - MANGANESE DEFICIENCY AND TOXICITY - 1984

Dietary deficiencies of manganese impair the insulin release and gluconeogenesis.

W-1) BIRD ET AL - EFFECT OF INHALATION OF MANGANESE IN RHESUS MONKEYS - 1984

Four female rhesus monkeys were exposed 6 hours a day, five days a week for two years to inhale manganese at a concentration of 30 mg per cubic meter. During life no abnormalities in behavior or neurological signs were noted. Accumulation of manganese in certain areas of the brain was noted. The authors suggest that higher concentrations over longer periods of time would be needed to cause detectible problems.

X-1) GRAHAM - MOLECULAR PATHOGENESIS OF MANGANESE NEUROTOXICITY AND PARKINSON'S - 1984

Additional review article on pathogenesis of Parkinson's disease, manganese toxicity and oxidative products of dopamine etc.

HH) EPA AIR DOCKET/REFS

This file contains a series of references obtained from POLTOX. It contains a reference Eriksson, H. et al study of four monkeys given a total of 8 g of manganese oxide by subcu injections that developed poisoning.
Quite a few references here, many of which are already recorded above.

LL) CHEMETALS - 11 JULY 90 REPORT

Chemetals draft statement dated July 11, 1990.

NN) TO: REILLY FROM: ANTHONY - LETTER

OO) TOXICANTS OCCURRING IN FOODS - NAS - 1966

PP) PARKINSON'S DISEASE - URBAN AND SCHWARZENBERG - 1988

Brief mention of manganese.

J-1) INFORMATION BULLETIN - SURVEY OF CHEMICALS BEING TESTED FOR CARCINOGENECITY - AUGUST 1979

Mentions both the Stenbach intratracheal and the Furst IM injection studies for cancer.

K-1) INFORMATION BULLETIN - SURVEY OF CHEMICALS BEING TESTED FOR CARCINOGENECITY - JANUARY 1978

Mentions additional studies by Shimkin and Stoner.

Y-1) SANO REFERENCES

A series of references.

AAA) ROTH REPORT WITH REFERENCES

BBB) COPPER REFERENCES

CCC) GREGUS AND KLAASEN - 1984

A study of manganese chloride deposition in rats.

DDD) CLAY AND MORRIS - 1989

CMT and MMT compared for lung toxicity in rats and suggestion made that monooxygenase metabolites released inorganic manganese within pulmonary cells.

EEE) NEWLAND ET AL - 1987

Two monkeys inhaled radio labeled manganese chloride and long (over one year) half life noted in brain.

FFF) WAALKES AND KLAASSEN - 1985

Deals with IP injections of manganese chloride in rats in relation to concentration of metallothionein.

MM) CANADA NRC

Comprehensive report with tables of air and water concentrations of manganese plus extensive article by Donaldson warning about potentional toxicity of manganese.

II) WORLD HEALTH ORGANIZATION - MANGANESE 1981

At present, there is no evidence that the manganese concentrations of less than 0.1 microgram/m3 generally found in ambient rural and urban air are associated with any health risk to man.

3
AU - Anonymous
TI - Manganese
SI - NIOSH/00193329/TOXLINE
SO - Environmental Health Criteria 17, IPCS International Programme on Chemical Safety, World Health Organisation, 110 pages, 477 references, 1981
AB - Properties and analytical methods for determining the presence of manganese (7439965), sources of manganese in the environment, environmental levels and exposure, transport and distribution in environmental media, metabolism of manganese, manganese deficiency, experimental studies on the effects on manganese, human epidemiological and clinical studies were reviewed, and an evaluation of the health risks to man from exposure to manganese and its compounds was presented. Most of the manganese produced in the world was used in the making of steel, either as ferromanganese, silicomanganese, or spiegeleisen. Manganese was also used in the production of nonferrous alloys, dry cell batteries, in fertilizers, animal feeds, pharmaceutical products, dyes, paint dryers, catalysts, wood preservatives, and in the glass and ceramic industries. Studies have indicated that chronic exposure is a hazard in the mining and processing of manganese ores and in these other industries. Manganese poisoning is characterized by psychological and neurological manifestations. Autopsy studies have revealed lesions on the central nervous system which are most severe in the striatum and pallidum. Individual susceptibility to the adverse effects of manganese varies considerably. Early diagnosis is difficult in the absence of reliable biological indicators of exposure. Adverse effects have been reported in populations particularly in areas associated with manganese processing facilities.

8
AU - Archibald FS
AU - Tyree C
TI - Manganese poisoning and the attack of trivalent manganese upon catecholamines
SI - CA/107/128592Q/TOXLIT
SO - Arch. Biochem. Biophys.; VOL 256, ISS 2, 1987,638-50
AB - CBAC COPYRIGHT: CHEM ABS Mn3+ was readily produced by O2- in vitro and spontaneously under conditions obtainable in the human brain. Mn3+ as its pyrophosphate complex rapidly and efficiently carried out 4-electron oxidns. of dopamine, its precursor DOPA, and its biosynthetic products epinephrine and norepinephrine. Mn3+-pyrophosphate specifically attacked dihydroxybenzene derivs., but only those with adjacent OH groups. Further, the addn. of Mn2+-pyrophosphate to a system contg. a flux of O2- and dopamine greatly accelerated the oxidn. of dopamine. The oxidn. of dopamine by Mn3+ neither produced nor required O, and Mn3+ was far more efficient than Mn2+, Mn4+ (MnO2), O2-, or H2O2 in oxidizing the catecholamines. A higher oxidn. state, Mn(OH)3,

formed spontaneously in an aq. Mn(OH)2 ppt. and slowly darkened, presumably being oxidized to MnO2. Like reagent MnO2, it weakly catalyzed dopamine oxidn. However, both MnO2 prepns. showed dramatically increased abilities to oxidize dopamine in the presence of pyrophosphate due to enhancement of the spontaneous formation of the Mn3+ complex. Apparently, the pathol. of Mn neurotoxicity is dependent on the ease with which simple Mn3+ complexes are formed under physiol. conditions and the efficiency with which they destroy catecholamines.

25
AU - ARCHIBALD FS
AU - TYREE C
TI - MANGANESE POISONING AND THE ATTACK OF TRIVALENT MANGANESE UPON CATECHOLAMINES
SI - BIOSIS/87/31561/TOXLINE
SO - ARCH BIOCHEM BIOPHYS; 256 (2). 1987. 638-650.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN NEUROTOXICITY PARKINSON'S DISEASE DOPAMINE

4
AU - Archibald FS
AU - Tyree C
TI - Manganese poisoning and the attack of trivalent manganese upon catecholamines.
UI - 87297553/BACK86
AB - Human manganese poisoning or manganism results in damage to the substantia nigra of the brain stem, a drop in the level of the inhibitory neurotransmitter dopamine, and symptoms resembling those of Parkinson's disease. Manganic (Mn3+) manganese ions were shown to be readily produced by O-2 in vitro and spontaneously under conditions obtainable in the human brain. Mn3+ as its pyrophosphate complex was shown to rapidly and efficiently carry out four-electron oxidations of dopamine, its precursor dopa (3,4-dihydroxyphenylalanine), and its biosynthetic products epinephrine and norepinephrine. Mn3+-pyrophosphate was shown to specifically attack dihydroxybenzene derivatives, but only those with adjacent hydroxyl groups. Further, the addition of Mn2+-pyrophosphate to a system containing a flux of O2- and dopamine greatly accelerated the oxidation of dopamine. The oxidation of dopamine by Mn3+ neither produced nor required O2, and Mn3+ was far more efficient than Mn2+, Mn4+ (MnO2), O2-, or H2O2 in oxidizing the catecholamines. A higher oxidation state, Mn(OH)3, formed spontaneously in an aqueous Mn(OH)2 precipitate and slowly darkened, presumably being oxidized to MnO2. Like reagent MnO2, it weakly catalyzed dopamine oxidation. However, both MnO2 preparations showed dramatically increased abilities to oxidize dopamine in the presence of pyrophosphate due to enhancement of the spontaneous formation of the Mn3+ complex. These results strongly suggest that the pathology of manganese neurotoxicity is dependent on the ease with which simple Mn3+ complexes are formed under physiological conditions and the

efficiency with which they destroy catecholamines.
SO - Arch Biochem Biophys 1987 Aug 1;256(2):638-50

18
AU - Barbeau A
TI - Manganese and extrapyramidal disorders. (A critical review and tribute to Dr. George C. Cotzias)
SI - CA/100/204572F/TOXLIT
SO - Neurotoxicology; VOL 5, ISS 1, 1984,13-35
AB - CBAC COPYRIGHT: CHEM ABS A review with many refs. on neurotoxicity of Mn in animals and man.

7
AU - Barbeau A
TI - Manganese and extrapyramidal disorders (a critical review and tribute to Dr. George C. Cotzias).
UI - 84192178/BACK83
AB - In this essay we first review the important contributions of Dr. George Cotzias to the understanding of chronic manganese intoxication and of manganese metabolism in man and animals. We also indicate the original contribution of Dr. John Donaldson to the mechanism of the neurotoxicity of manganese. In a second phase, the author challenges the tenet that Parkinson's disease is a form of chronic manganese intoxication and that manganism is an experimental model for Parkinson's disease. Clinical, pathological, experimental and biochemical evidence are brought to bear on this argument. Thirdly the author proposes that the necessary event to the so-called "depigmentation: of the substantia nigra and subsequent bradykinetic "low dopamine: syndrome is an early enhanced turnover of dopamine. Manganese intoxication is only one of the factors which may serve as a trigger to this event. Many others are also listed. In opposition to current views, who look for causal factors in Parkinson's disease along the pathways for melanogenesis, the author thus proposes a novel hypothesis which envisions a variety of transient "trigger factors: acting at the dopamine synapse to increase dopamine turnover. In turn, this increased synthesis of dopamine favours the production of large quantities of free radicals within the cell bodies in the substantia nigra, eventually overflowing the scavenging capacity of neuromelanin and their protective barrier, and causing cell death. The resulting decreased pool of dopamine-producing cells leads to a self-perpetuating situation of ever increasing demand on the remaining cells, and "progression: of the disease. Finally the author stresses the fact that genetic factors may play a role in an individual's susceptibility to such triggers. Again defective manganese transport, metabolism or binding are only some of the mechanisms possibly underlying such genetic predisposition to induced basal ganglia disorders. Further studies relating to manganese in these disorders and particularly in Parkinson's disease should focus not on the "intoxication: part of the overload and its striatopallidal consequences, but on the

intimate mechanism of destabilization of the homeostatic regulator in neuromelanin bearing cells, even after the exposure period.
SO - Neurotoxicology 1984 Spring;5(1):13-35

64
AU - Berlin M
AU - Lee IP
AU - Russell LD
TI - Effects Of Metals On Male Reproduction
SI - NIOSH/00156214/TOXLINE
SO - Reproductive and Developmental Toxicity of Metals, Clarkson, T. W., G. F. Nordberg, and P. R. Sager, Editors; Plenum Press, New York, pages 29-40, 44 references, 19831983
AB - The effects of environmental metal exposure on human male reproductive function are reviewed. There is little direct evidence of specific toxic effects. Data from animal studies is examined. Potential areas of interaction having health significance for humans are identified and expected effects are described. Indirect effects on male reproductive organs are discussed. Lead (7439921) or cadmium (7440439) may have effects on the hypothalamus or pituitary and lead, mercury (7439976), or manganese (7439965) may interfere with nervous function. Direct effects on male reproductive organs are discussed in terms of specific target organs. A number of metals are reported to accumulate in the interstitial tissue of the testes in animals. Mercury compounds, lead, manganese, cesium (7440462), and plutonium (7440075) have been observed in the seminiferous tubules, but the effects on spermatogonia or primary spermatocytes are unknown. Lead, arsenic (7440382), or cadmium may affect accessory sex organs. Changes in semen quality have been seen in animals after exposure to lead, manganese, and mercury compounds, and teratological studies indicate toxic effects of lead, mercury compounds, and boron (7440428). The authors conclude that although there is little data on the effects of metal exposure on reproductive function in human males, there is enough indirect evidence of adverse effects to warrant recommending carefully controlled comprehensive studies.

6
AU - Bird ED
AU - Anton AH
AU - Bullock B
TI - The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey.
UI - 84192182/BACK83
AB - Manganese (Mn) may produce neurotoxicity in man through inhalation of Mn dust. Animals exposed to excessive Mn develop neurological abnormalities, and neuropathological lesions in the brain mainly in the globus pallidus with decreased concentrations of the neurotransmitter, dopamine (DA), in the brain. Monkeys exposed to Mn by inhalation did not produce any abnormal

movements. After two years, the animals were sacrificed and certain brain areas were compared to controls. There were significant decreases in DA concentration in caudate and globus pallidus, and there was a 60-80% increase in Mn concentration in the basal ganglia of the brain. The DA system in the basal ganglia is vulnerable to the effects of Mn, but the amount of Mn inhaled and the period of exposure would appear to determine whether abnormal neurological signs develop.
SO - Neurotoxicology 1984 Spring;5(1):59-65

47
AU - BIRD ED
AU - ANTON AH
AU - BULLOCK B
TI - The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey.
SI - HEEP/84/12140/TOXLINE
SO - NEUROTOXICOLOGY (LITTLE ROCK); 5 (1). 1984. 59-66.
AB - HEEP COPYRIGHT: BIOL ABS. Mn may produce neurotoxicity in man through inhalation of Mn dust. Animals exposed to excessive Mn develop neurological abnormalities, and neuropathological lesions in the brain mainly in the globus pallidus with decreased concentrations of the neurotransmitter, dopamine (DA), in the brain. Monkeys exposed to Mn by inhalation did not produce any abnormal movements. After 2 yr, the animals were sacrificed and certain brain areas were compared to controls. There were significant decreases in DA concentration in caudate and globus pallidus, and there was a 60-80% increase in Mn concentration in the basal ganglia of the brain. The DA system in the basal ganglia was vulnerable to the effects of Mn, but the amount of Mn inhaled and the period of exposure appeared to determine whether abnormal neurological signs developed.

52
AU - Bleecker ML
TI - Parkinsonism: A Clinical Marker of Exposure to Neurotoxins
SI - NIOSH/00185805/TOXLINE
SO - Neurotoxicology and Teratology, Vol. 10, No. 5, pages 475-478, 61 references, 19881988
AB - Parkinsonism as a clinical marker of exposure to neurotoxins was discussed. The nature of Parkinson's disease and its relationship to the effects of neurotoxic compounds were summarized. Parkinson's disease results from a loss of dopaminergic cells in the substantia nigra and degenerative changes in other pigmented nuclei in the brain stem, especially the locus ceruleus. Exposure to a variety of neurotoxic agents such as carbon-monoxide (630080), carbon-disulfide (75150), manganese (7439965) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (28289545) (MPTP) can induce parkinsonian symptoms. Parkinsonian symptoms associated with carbon-monoxide intoxication were discussed. Delayed encephalopathy frequently accompanied by parkinsonism is

the most frequent neurological sequela associated with acute carbon-monoxide poisoning. It results from brain hypoxia or anoxia. Carbon-monoxide induced parkinsonism is associated with lesions on the globus pallidus. Manganese toxicity was discussed. Chronic manganism produces an irreversible syndrome that closely resembles Parkinson's disease. The neuropathological features, however, are very different. Whereas Parkinson's disease affects the substantia nigra, manganism affects the striatum and globus pallidus. Carbon-disulfide toxicity was discussed. Carbon-disulfide induced neuropathy resembles that of Parkinson's disease; however, it affects the output structures of the basal ganglia like that of manganism rather than the input structures characteristic of true Parkinson's disease. MPTP toxicity was discussed. MPTP produces all of the major features of Parkinson's disease. Humans with MPTP induced parkinsonism respond to the same antiparkinsonism agents in the same way as patients with manganese induced parkinsonism. The major pathological change induced by MPTP is a degeneration of dopaminergic neurons in the substantia nigra. The author concludes that parkinsonism can be regarded as a clinical marker of neurotoxin exposure, although it is associated with a wide variety of neuropathological mechanisms.

1
AU - Braitman DJ
AU - Coyle JT
TI - Inhibition of [3H]kainic acid receptor binding by divalent cations correlates with ion affinity for the calcium channel.
AD - Department of Environmental Health Sciences, Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MA 21205.
UI - 88039371/BACK86
AB - Since the neurotoxicity of kainic acid may be due to the opening of membrane channels for calcium ions for (Ca2+), the effects of Ca2+ and other cations were examined on the specific binding of [3H]kainic acid to membranes from the forebrain of the rat. [3H]Kainic acid bound to a high affinity site (KD = 5.6 nM) that was inhibited in a concentration-dependent manner by Ca2+ ions with an IC50 of 3.2 mM. In the presence of 1 mM Ca2+, the KD of the binding of [3K]kainic acid increased to 11.1 nM without any change in the Bmax. The divalent cations, manganese and cobalt, also were potent inhibitors of the binding of [3H]kainic acid, while barium and strontium were much weaker. The inhibitory effects of Ca2+ on the binding of [3H]kainic acid were blocked by the inorganic Ca2+ channel blockers, cadmium and lanthanum. These data suggest that Ca2+ modulates the binding affinity [3H]kainic acid through an allosteric interaction between the binding site on the Ca2+ channel and the kainic acid receptor.
SO - Neuropharmacology 1987 Sep;26(9):1247-51

38
AU - BRENNAN CE

AU - NACHTMAN JP
TI - MANGANESE NEUROTOXICITY EVIDENCE FOR OXYGEN DEPENDENT EFFECT ON DOPAMINE AUTOOXIDATION
SI - BIOSIS/86/22657/TOXLINE
SO - 70TH ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ST. LOUIS, MO., USA, APR. 13-18, 1986. FED PROC; 45 (3). 1986. 440.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT PARKINSONISM

66
AU - Chandra SV
AU - Murthy RC
TI - Neurotoxic Effects Due To Lead And Manganese Interaction
SI - NIOSH/00137183/TOXLINE
SO - National Conference on Lead, Zinc and Cadmium at Workplace: Environment and Health Care, Vol. 1, Indian Lead Zinc Centre, pages 1.9-1.15, 9 references, 19831983
AB - The neurotoxicological effects of exposure to both lead (7439921) and manganese (7439965) were investigated. ITRC-rats were given 3 milligrams per milliliter (mg/ml) manganese in water. Three groups of rats were also given 5, 8, and 12mg per kilogram (kg) lead, intraperitoneally (ip). Three groups were given identical doses of lead alone. Controls were given sodium-chloride (7647145) ip and in drinking water. The study lasted 14 days. Animals were killed and dopamine (51616), norepinephrine (51412), and 5-hydroxytryptamine (50679) (5-HT) were determined. Accumulation of metals in the brain was measured. Manganese alone produced significant increases in brain dopamine and norepinephrine. Administration of 5mg/kg lead had no effect on biogenic amines. Lead alone at the two higher doses caused a decrease in dopamine and 5-HT and an increase in norepinephrine. When exposed to lead and manganese a significant decrease in the contents of dopamine, norepinephrine, and 5-HT was observed with the higher doses of lead. Accumulation of manganese in the brain increased significantly when given alone or simultaneously with lead. Exposure to lead alone produced a dose related increase in its accumulation in the brain. However, when the rats were coexposed to lead and manganese, the lead accumulated to a greater extent than after lead alone. The authors conclude that the interactions of metals produce neurological damage even after a short exposure period.

67
AU - Dehaven DL
AU - Mailman RB
TI - The Use Of Radioligand Binding Techniques In Neurotoxicology
SI - NIOSH/00149642/TOXLINE
SO - Reviews in Biochemical Toxicology, Vol. 5, pages 193-238, 196 references, 19831983
AB - The use of radioligand binding techniques to evaluate neurotoxicity is reviewed. Binding sites and receptors are defined. Central nervous system receptors that have been studied

rather extensively include the biogenic amines, amino acids, and acetylcholine. The role of neuropeptide receptors is being examined. Radioligand methodology is considered a direct means for evaluating the binding ability of some toxicants or estimating changes in the receptors induced by toxicants. Displacement and saturation assays are models for the study of neurotoxicity. Data on in-vivo radioreceptor assays in neurobiology is reviewed. The strengths and weaknesses of the methodology are described. Receptor binding effects of toxicants such as acrylamide (79061), heavy metals such as lead (7439921), manganese (7439965) and cadmium (7440439), organophosphate pesticides such as diisopropylfluorophosphate (55914), Kepone (143500) and disulfoton (298044), and some miscellaneous compounds are presented. The authors conclude that radioreceptor assays alone cannot determine the actions of a toxicant. An integrated approach that includes studies of metabolism, pharmacology, and other factors provides the greatest opportunity for determining how a neurotoxicant affects the central nervous system.

6
AU - Ding X
AU - Liu C
AU - Dong J
AU - Yuan S
TI - Toxic action of manganese on dopamine receptors in rat striatum
SI - CA/108/181626A/TOXLIT
SO - Zhongguo Yaolixue Yu Dulixue Zazhi; VOL 1, ISS 3, 1987,161-5
AB - CBAC COPYRIGHT: CHEM ABS Rats were treated for 10 consecutive days by i.p. injection of $MnSO_4$ at 15 or 30 mg/kg. Twenty-four hours after the last dose, no significant differences in the body, brain, and striatum wts. were obsd. between the control and Mn-treated rats. DNA or RNA decreased and protein/DNA ratio increased significantly in striatum in high-dose Mn-treated rats but not in low-dose Mn-treated rats. In high-dose Mn-treated rats, swelling of some mitochondria was obsd. in the dopaminergic neuron under electron microscopy. The major increase in the binding of the dopaminergic antagonist [3H]spiperone to striatum revealed changes in both the dissocn. const. (KD), which decreased significantly in Mn-treated rats (from 4.32 to 3.67 nM) and in the receptor site d. (Bmax), which increased in Mn-treated rats (from 589 to 692 fmol/mg protein). Mn exposure produced a marked and dose-dependent increase in striatal and synaptic Mn, assocd. with a consistent elevation in the binding of the [3H]spirerone to striated membranes. The presence of excess Mn in the striatum and synapses presumably leads to an alteration in the function of the dopaminergic receptor. The results suggested a sensitivity of dopaminergic pathway to Mn toxicity in the nervous system and an involvement of the dopaminergic system in neurotoxicity of Mn.

24

AU - Donaldson J
AU - McGregor D
AU - LaBella F
TI - Manganese neurotoxicity: a model for free radical mediated neurodegeneration?
SI - CA/097/209925C/TOXLIT
SO - Can. J. Physiol. Pharmacol.; VOL 60, ISS 12, 1982,1398-405
AB - CBAC COPYRIGHT: CHEM ABS Mn neurointoxication in neonatal rats resulted in significant depression of lipid peroxidn. in several rat brain regions examd. In the striatum, lipid peroxidative activity was abolished, an effect which may be related to alteration in neurotransmitters often obsd. in the striatum of Mn-treated rats. The chronic, extrapyramidal stage of manganism, may ensue when excess Mn is oxidized to higher valency forms where it can potentiate the autoxidn. of catecholamines, like dopamine, resulting in concomitant formation of free radicals and cytotoxic quinones. This latter effect may arise preferentially in the substantia nigra, where neuromelanin is formed nonenzymically by autoxidn. of dopamine.

33
AU - DONALDSON J
AU - BARBEAU A
TI - MANGANESE NEUROTOXICITY POSSIBLE CLUES TO THE ETIOLOGY OF HUMAN BRAIN DISORDERS
SI - BIOSIS/86/10131/TOXLINE
SO - GABAY, S., J. HARRIS AND B. T. HO (ED.). NEUROLOGY AND NEUROBIOLOGY (NEW YORK), VOL. 15. METAL IONS IN NEUROLOGY AND PSYCHIATRY. XIII+409P. ALAN R. LISS, INC.: NEW YORK, N.Y., USA. ILLUS. ISBN 0-8451-2717-9.; 0 (0). 1985. 259-286.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM

63
AU - Donaldson J
AU - McGregor D
AU - LaBella F
TI - Manganese Neurotoxicity: A Model For Free Radical Mediated Neurodegeneration
SI - NIOSH/00161236/TOXLINE
SO - Canadian Journal of Physiology and Pharmacology, Vol. 60, No. 11, pages 1398-1405, 46 references, 19821982
AB - Some effects of manganese (16397914) on the central nervous system were investigated in rats. Neonatal Sprague-Dawley-rats received daily injections of a control saline solution or 20 micrograms per gram body weight manganese-chloride (7773015) for 14 days. Rats were then killed and brains removed. The effects of manganese on central nervous system lipid peroxidation were observed through the malondialdehyde (542789) produced as an indicator of free radical activity. Individual regions of the brain were studied. Other male Sprague-Dawley-rats were injected intracerebroventricularly with saline or 25 micrograms manganese-chloride. At 1 hour animals were killed and the

norepinephrine contents determined. There was considerable variation in the lipid peroxidation in various brain regions of newborn rats. High activity was found in the cerebellum and the hypothalamus, compared with the medulla oblongata and the midbrain. Treatment with manganese resulted in a drastic fall in lipid peroxidation which ranged from about 40 percent in the olfactory bulb to almost 100 percent in the striatum. The contents of norepinephrine fell significantly in the hypothalamus of manganese treated rats. The authors conclude that manganese reduces lipid peroxidation and the synthesis of norepinephrine in the rat brain.

7
AU - Donaldson J
TI - The physiopathologic significance of manganese in brain: its relation to schizophrenia and neurodegenerative disorders
SI - CA/107/169988S/TOXLIT
SO - Neurotoxicology; VOL 8, ISS 3, 1987,451-62
AB - CBAC COPYRIGHT: CHEM ABS A review with 48 refs. of etiol. and clin. patterns of Mn psychosis; Mn neurotoxicity in animals; dopamine oxidn. as a mechanism of Mn neurotoxicity; the protective effect of Zn- or Mn-induced dopamine oxidn.; ecotoxicol. of Mn and the Groote Eylandt syndrome; Mn- and MPTP-induced hyperglycemia in mice; and selective Mn toxicity to tissues with elevated oxidases and H2O2 content.

56
AU - Donaldson J
TI - The Physiopathologic Significance of Manganese in Brain: Its Relation to Schizophrenia and Neurodegenerative Disorders
SI - NIOSH/00172068/TOXLINE
SO - NeuroToxicology, Vol. 8, No. 3, pages 451-462, 48 references, 19871987
AB - The physiopathology of elevated brain manganese (7439965) (Mn) was reviewed with the purpose of elucidating mechanisms of Mn neurotoxicity. Animal models of Mn pathology, case studies of Locura-manganica or manganese madness, the Groote Eylandt syndrome, chronic manganism, and manganese psychosis were discussed. Common observations included melanin loss, degeneration of the striatum or its components, and alterations in central dopaminergic receptors implying dopamine oxidation as a mechanism of Mn pathology. Hypotheses for Mn pathology reviewed included Mn induced enhancement of dopamine autooxidation, Mn catalyzed production of toxic catecholamines, Mn self oxidation and dismutation with resulting oxidative destruction of dopamine, and catecholamine oxidation by trivalent Mn. The role of zinc in protecting against Mn induced dopamine oxidation was attributed to the affinity of zinc ions for hydroxyl moieties and to the involvement of zinc in maintaining redox balance and membrane stability. The author suggests that tissue susceptibility to Mn toxic effects in the brain are related to the redox bioenergetic status of the various tissues

and that other tissues with elevated levels of oxidative enzymes (oxidases, peroxides) such as testes, pancreatic-B cells, and macrophages would show similar sensitivity to Mn insult.

12
AU - Donaldson J
AU - Barbeau A
TI - Manganese neurotoxicity: possible clues to the etiology of human brain disorders
SI - CA/104/001754B/TOXLIT
SO - Neurol. Neurobiol.; VOL 15, ISS Met. Ions Neurol. Psychiatry, 1985,259-85
AB - CBAC COPYRIGHT: CHEM ABS A review with 70 refs. on exptl. induced manganism, chronic Mn neurointoxication, physiol. significance of Mn in brain, and free radicals in neurodegenerative disorders.

50
AU - DONALDSON J
AU - LABELLA FS
AU - GESSER D
TI - Enhanced autoxidation of dopamine as a possible basis of manganese neurotoxicity.
SI - HEEP/81/09788/TOXLINE
SO - NEUROTOXICOLOGY (PARK FOR SOUTH); 2 (1). 1981. 53-64.
AB - HEEP COPYRIGHT: BIOL ABS. Autoxidation of dopamine as measured by its aminochrome formation at 480 nm was considerably potentiated by Mn++ compared to other biologically-important divalent cations (Cu++, Zn++, Ni++, Ca++ and Mg++). Effectiveness of autoxidation by metal ions was closely related to their redox potential. Mn enhanced autoxidation of dopamine was associated with increased generation of free radicals O2-, H2O2 and HO as suggested by inhibitory effects of superoxide dismutase, catalase and ethanol. Mn, by enhancing oxidation of dopamine, augmented considerably the production of neurotoxins emanating from this process and under in vivo conditions could be expected to contribute significantly to neurodegenerative changes that accompany Mg dyskinesia in man.

28
AU - DYKENS JA
AU - SULLIVAN SG
AU - STERN A
TI - OXIDATIVE REACTIVITY OF THE TRYPTOPHAN METABOLITES 3 HYDROXYANTHRANILATE CINNABARINATE QUINOLINATE AND PICOLINATE
SI - BIOSIS/87/12710/TOXLINE
SO - BIOCHEM PHARMACOL; 36 (2). 1987. 211-218.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM NEUROTOXICITY CARCINOGENICITY HEMOGLOBIN MANGANESE OXYGEN

44
AU - ERIKSSON H

AU - MORATH C
AU - HEILBRONN E
TI - EFFECTS OF MANGANESE ON THE NERVOUS SYSTEM
SI - HEEP/85/05699/TOXLINE
SO - 1983 SWEDISH NEUROTOXICOLOGY SYMPOSIUM, COPENHAGEN, DENMARK, APR. 14-16, 1983. ACTA NEUROL SCAND SUPPL; 70 (100). 1984. 89-94.
AB - HEEP COPYRIGHT: BIOL ABS. RRM RAT CYTOTOXICITY NEUROTOXICITY THIOL

55
AU - Eriksson H
AU - Magiste K
AU - Plantin L-O
AU - Fonnum F
AU - Hedstrom K-G
AU - Theodorsson-Norheim E
AU - Kristensson K
AU - Stalberg E
AU - Heilbronn E
TI - Effects of Manganese Oxide on Monkeys as Revealed by a Combined Neurochemical, Histological and Neurophysiological Evaluation
SI - NIOSH/00176589/TOXLINE
SO - Archives of Toxicology, Vol. 61, No. 1, pages 46-52, 41 references, 19871987
AB - The neurochemical, neurophysiological, and histological effects of high doses of manganese-oxide (1317357) were studied in monkeys. Manganese-oxide was administered by subcutaneous injection in a suspension of olive-oil. The animals received a total of 8 grams of manganese (7439965) over 5 months. Evaluation parameters included animal behavior as recorded on videotape, manganese levels in various brain areas, monoamine analysis, enzymatic activities of DOPA-decarboxylase (DDC), choline-acetyltransferase (CAT), and glutamic-acid-decarboxylase (GAD), glutathione analysis, and needle electromyographic analysis of the tibial anterior and quadriceps femoris muscles after stimulation of the peroneal nerve. Behavioral changes included established hyperactivity after 2 months and hypoactivity after 5 months. Motor weakness, tremor, and myoclonus were observed during the later stages. Exposed monkeys showed significant losses of neurons and concomitant astrogliosis in the pallidum. Blood manganese levels were approximately 20 times the control values throughout the experiment, and different brain regions showed different susceptibilities to manganese uptake. The highest levels of brain manganese were reported in the globus pallidus, caudate nucleus, substantia nigra, cerebral cortex, and cerebellum, and significant reductions of dopaminergic and serotoninergic chemicals were observed in these areas. The activities of DDC and CAT were reduced in the putamen and globus pallidus, and the activity of GAD appeared unaffected by the treatment. Brain glutathione levels were depressed in the manganese exposed animals. There was no evidence of peripheral neuropathy or disturbed neuromuscular transmission.

31
AU - EWERS U
AU - SCHLIPKOETER H-W
TI - CHRONIC TOXICITY OF METALS IN HUMANS
SI - BIOSIS/86/36509/TOXLINE
SO - MERIAN, E. (ED.). METALLE IN DER UMWELT: VERTEILUNG, ANALYTIK UND BIOLOGISCHE RELEVANZ (METALS IN THE ENVIRONMENT: DISTRIBUTION, ANALYSIS AND BIOLOGICAL RELEVANCE). XVII+722P. VCH VERLAGSGESELLSCHAFT/PHYSIK-VERLAG: WEINHEIM, WEST GERMANY; DEERFIELD BEACH, FLA., USA. ILLUS. ISBN 3-527-25817-5.; 0 (0). 1984 (RECD. 1986). 229-236.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM WORKER ARSENIC LEAD MERCURY TETRAETHYLLEAD MANGANESE THALLIUM TIN SELENIUM DERMAL TOXICITY HEPATOTOXICITY HEMOTOXICITY NEPHROTOXICITY NEUROTOXICITY CARDIOVASCULAR TOXICITY

7
AU - Ferraz HB
AU - Bertolucci PHF
AU - Pereira JS
AU - Lima JGC
AU - Andrade LAF
TI - Chronic Exposure to the Fungicide Maneb May Produce Symptoms and Signs of CNS Manganese Intoxication
SI - NIOSH/00191327/TOXLINE
SO - Neurology, Vol. 38, No. 4, pages 550-553, 32 references, 1988
AB - A study of neurological symptoms in workers exposed to maneb (12427382) was conducted. The impetus for the study was the development of Parkinsonian symptoms in two Brazilian agricultural workers who had been exposed to maneb. The cohort consisted of 50 male agricultural workers, mean age 37 years, from Ibiuna, Brazil who had been exposed to maneb for at least 6 months. The comparisons consisted of 19 rural workers, mean age 24 years, who had not been exposed to maneb. The subjects completed a questionnaire seeking information on occupational history and the occurrence of any central nervous system symptoms. They were given neurological examinations. Blood samples were collected and analyzed for manganese (7439965). The prevalence of neurological symptoms such as plastic rigidity with cogwheel phenomena, headache, fatigue, nervousness, memory impairment, and sleepiness was significantly higher in the subjects exposed to maneb than in the comparisons; however, no clustering of signs or symptoms was seen. The mean blood manganese concentrations in the exposed and comparison subjects were 7.7 and 8.8 nanograms per 100 milliliter, respectively. The difference was not statistically significant. Blood manganese concentrations did not differ significantly between those with and those without neurological signs. The authors suggest that occupational exposure to maneb may be involved in human chronic manganese poisoning.

6
AU - Florence TM
AU - Stauber JL
TI - Neurotoxicity of manganese [letter]
SO - Lancet 1988 Feb 13;1(8581):363

11
AU - Garner CD
AU - Nachtman JP
TI - Manganese Catalyzed Auto-oxidation of Dopamine to 6-Hydroxydopamine In Vitro
SI - NIOSH/00188855/TOXLINE
SO - Chemico-Biological Interactions, Vol. 69, No. 4, pages 345-351, 19 references, 1989
AB - The effect of manganese (7439965) on the autooxidation of dopamine to 6-hydroxydopamine (OHdopamine) was studied in-vitro. Dopamine at 0.25 millimoles per liter was incubated with 0.05 millimolar (mM) manganese as manganese(II)-chloride (7773015) in a Tris buffer, pH 7.8, at 37 degrees-C for up to 60 minutes. Aliquots were taken after 1, 15, 30, or 60 minutes incubation and analyzed for OHdopamine by a high performance liquid chromatographic technique. Manganese caused a rapid autooxidation of dopamine, a large quantity of OHdopamine being detected within 1 minute. No dopamine remained in the reaction mixture after 30 minutes. When manganese was absent, only 11 percent of the initial concentration of dopamine disappeared after 60 minutes. No OHdopamine was detected. The authors conclude that OHdopamine is a product of manganese catalyzed dopamine autooxidation. Since OH dopamine is a known neurotoxicant that exerts its effects on dopamine nerve terminals, in-vivo formation of OHdopamine could be involved in the mechanism by which manganese exerts its neurotoxic effects.

1
AU - Gianutsos G
AU - Seltzer MD
AU - Saymeh R
AU - Wu ML
AU - Michel RG
TI - Brain manganese accumulation following systemic administration of different forms.
UI - 86129894/BACK83
AB - The content and retention of manganese in the blood and brain of mice exposed to different forms of the metal was compared. Mice received an acute sc injection of manganese as the chloride or oxide (Mn3O4) or as the organic MMT. A single injection markedly elevated brain manganese concentrations within 1 day and elevated levels were maintained for at least 21 days. Repeated injections led to further increases in both brain and blood, although the levels in the brain appeared to persist at consistently high levels for longer periods. The chloride form produced higher brain levels than either of the other two forms. These results

appear to suggest that the slowly developing neurotoxicity in response to manganese exposure may be due to a persistent retention of manganese by the brain.
SO - Arch Toxicol 1985 Sep;57(4):272-5

35
AU - GIANUTSOS G
AU - SELTZER MD
AU - SAYMEH R
AU - WU M-L W
AU - MICHEL RG
TI - BRAIN MANGANESE ACCUMULATION FOLLOWING SYSTEMIC ADMINISTRATION OF DIFFERENT FORMS
SI - BIOSIS/86/07087/TOXLINE
SO - ARCH TOXICOL; 57 (4). 1985. 272-275.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM MOUSE NEUROTOXICITY

65
AU - Gianutsos G
AU - Seltzer MD
AU - Saymeh R
AU - Wang Wu M-L
AU - Michel RG
TI - Brain Manganese Accumulation Following Systemic Administration Of Different Forms
SI - NIOSH/00154536/TOXLINE
SO - Archives of Toxicology, Vol. 57, No. 4, pages 272-275, 11 reference, 19851985
AB - Blood and brain accumulation of manganese (7439965) was studied in mice. Male CD-1-mice were injected subcutaneously (sc) with manganese-dichloride (7773015), manganese-oxide (11129605), or methylcyclopentadienyl-manganese-tricarbonyl (12108133) in doses corresponding to 0.2 or 0.4 milliequivalent of manganese per kilogram (meq/kg). The mice were killed 2 hours to 21 days after injection. Blood and brain managanese concentrations were measured. Mice were given one to three weekly sc injections of 0.4meq/kg managanese as manganese-oxide or manganese-chloride. Blood and brain manganese concentrations were determined as before. Brain manganese concentrations were elevated to at least twice the control value 4 to 8 hours after administration, regardless of the chemical form of manganese injected. Blood manganese concentrations reached their maximum value 4 hours after injection of the oxide and remained elevated for 1 week. Blood manganese concentrations after manganese-chloride injection peaked at more than 10,000 percent of the control value within 1 hour and gradually declined over the course of 1 week; however, they were still 740 percent of the control value after 1 week. Peak brain concentrations occurred 24 hours after injection and remained elevated for at least 1 week. Repeated injections caused further increases in both brain and blood manganese concentrations. Elevated brain manganese concentrations after repeated injections decreased more slowly than after a single

injection. Brain manganese concentrations after 21 days were comparable to those observed 1 week after a single injection. The authors suggest that the slowly developing neurotoxicity in response to manganese exposure may be due to prolonged retention of manganese by the brain.

13
AU - Gianutsos G
AU - Seltzer MD
AU - Saymeh R
AU - Wu ML Wa
AU - Michel RG
TI - Brain manganese accumulation following systemic administration of different forms
SI - CA/103/191125X/TOXLIT
SO - Arch. Toxicol.; VOL 57, ISS 4, 1985,272-5
AB - CBAC COPYRIGHT: CHEM ABS The content and retention of Mn in the blood and brain of mice exposed to different forms Mn was compared. Mice received a s.c. injection of MnCl2, Mn3O4, or MMT [12108-13-3]). A single injection markedly elevated brain Mn concns. within 1 day and elevated levels were maintained for at least 21 days. Repeated injections led to further increases in brain and blood, although the levels in the brain appeared to persist at consistently high levels for longer periods. MnCl2 produced higher brain levels than the other 2 forms. Thus, the slowly developing neurotoxicity in response to Mn exposure may be due to a persistent retention of Mn by the brain.

71
AU - Gianutsos G
AU - Murray MT
TI - Alterations In Brain Dopamine And GABA Following Inorganic Or Organic Manganese Administration
SI - NIOSH/00140115/TOXLINE
SO - Neurotoxicology, Vol. 3, No. 3, pages 75-82, 24 references, 19821982
AB - The effects of manganese-chloride (7773015) (MnCl2) and methylcyclopentadienyl-manganese-tricabonyl (12108133) (MMT) on brain dopamine (DA) and gamma-aminobutyric-acid (GABA) were investigated in male CD-1 mice. Mice received 4 percent MnCl2 in diets for 6 months or MMT subcutaneously at 10, 20, and 80 milligrams per kilogram (mg/kg) on alternate days for 3 weeks. Controls received subcutaneous injections of propylene-glycol. After treatment mice were killed and brain GABA was assayed. DA and choline-acetyltransferase (CAT) were measured. MnCl2 administered in the feed reduced brain DA concentrations significantly. The DA of striatum nigra and olfactory tubercles were reduced by 21.5 and 18 percent, respectively, compared with controls. No changes were seen after 1 or 2 months. MMT injected at 20 and 80mg/kg reduced striatal DA by 10 and 23 percent, respectively. The olfactory tubercle was more resistant to the DA depleting effects of MMT. MnCl2 elevated

concentrations of GABA in striatum and substantia nigra, while MMT produced a similar effect but only at 80mg/kg dose. The cerebellum concentration of GABA was not affected by either compound. Acute injection of MMT failed to alter GABA concentrations in the brain. CAT remained unchanged in all regions of the brain after MnCl2 treatment, suggesting that cholinergic neurons were spared the neurotoxic effects of manganese. The authors conclude that long term treatments with MnCl2 and MMT induce changes in neurotransmitter concentrations.

16
AU - Graham DG
TI - Catecholamine toxicity: a proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease
SI - CA/101/067062U/TOXLIT
SO - Neurotoxicology; VOL 5, ISS 1, 1984,83-95
AB - CBAC COPYRIGHT: CHEM ABS A review and discussion with 22 refs. An hypothesis is presented which attempts to relate the pathogenesis of Mn neurotoxicity and Parkinson's disease to cytotoxicity from products of catecholamine oxidn.

4
AU - Graham DG
TI - Catecholamine toxicity: a proposal for the molecular pathogenesis of manganese neurotoxicity and Parkinson's disease.
UI - 84192185/BACK83
AB - An hypothesis is presented which attempts to relate the pathogenesis of both manganese neurotoxicity and Parkinson's disease to cytotoxicity from products of catecholamine oxidation. These include the products resulting from the partial reduction of oxygen (superoxide anion, hydroxyl radical, and hydrogen peroxide) and the semiquinones and ortho quinones produced during autoxidation or oxidation of catecholamines initiated by trivalent manganese.
SO - Neurotoxicology 1984 Spring;5(1):83-95

1
AU - Graham DG
TI - Comment on the commonality of manganese neurotoxicity and Parkinson's disease [letter]
SO - Neurotoxicology 1981 Oct;2(2):387-8

68
AU - Graham DG
TI - Catecholamine Toxicity: A Proposal For The Molecular Pathogenesis Of Manganese Neurotoxicity And Parkinson's Disease
SI - NIOSH/00143684/TOXLINE
SO - NeuroToxicology, Vol. 5, No. 1, pages 83-95, 22 references, 19841984
AB - The autooxidation and cytotoxicity of polyphenols and the sulfhydryl reactivity of their quinones were examined in humans. The locus ceruleus and substantia nigra regions of the brain were

examined in patients 6 to 10, 36 to 40, and 71 to 75 years old for the presence of neuromelanin (NM). Two patients from each group, free of neurological disease, were selected. The rate of polyphenol autoxidation was determined spectrophotometrically. Inhibition of labeled thymidine incorporation into DNA by neuroblastoma cells was used as a sensitive index of cell injury. Relative activity of quinone species and sulfhydryl reagents was assessed by reacting the quinone with alpha class DNA polymerase. Both locus ceruleus and substantia nigra showed greater concentrations of NM in the patients over 40 than in those less than 10. Among the polyphenol derivatives, dopamine (51616) (DA) was found to be more toxic than the beta hydroxylated catecholamines norepinephrine (51412) (NE) and epinephrine (51434) in the cells, suggesting that DA is readily oxidized. The most toxic species were the trihydroxy phenols, 6-hydroxydopamine (1199184) (6-HDA) and 2,3,5-trihydroxyphenylalanine (topa). Topa and 6-HDA also showed the highest autooxidation rates. The rate of autooxidation was found to correlate with the cytotoxicity of the polyphenols as shown by inhibition of thymidine incorporation into DNA. NE was minimally toxic and provided protection against 6-HDA and topa toxicity. The author concludes that the polyphenols produce cytotoxic effects through generations of such oxidative species as superoxide anions, hydroxyl radicals, and hydrogen-peroxide (7722841).

25
AU - Graham DG
TI - Comment on the commonality of manganese neurotoxicity and Parkinson's disease
SI - CA/096/063711K/TOXLIT
SO - Neurotoxicology (Park Forest South, Ill.); VOL 2, ISS 2, 1981,387-8
AB - CBAC COPYRIGHT: CHEM ABS A discussion with 2 refs. Review manganese neurotoxicity Parkinson disease

59
AU - Gresham LS
AU - Molgaard CA
AU - Golbeck AL
AU - Smith R
TI - Amyotrophic Lateral Sclerosis and Occupational Heavy Metal Exposure: A Case Control Study
SI - NIOSH/00168670/TOXLINE
SO - Neuroepidemiology, Vol. 5, No. 1, pages 29-38, 28 references, 19861986
AB - Retrospective case control studies were carried out in a population of 66 patients affected by amyotrophic lateral sclerosis (33 men averaging 55.2 years of age at diagnosis and 33 women averaging 57.7 years of age) and 66 comparisons matched for sex and age. Patients and comparisons completed a self administered questionnaire on race, sex, marital status, military

status, history of occupational exposure to nine heavy metals and other environmental and medical features. No significant differences were found between patients and comparisons as to ethnicity, history of military service, marital status and education. Only two females reported occupational exposure to lead (7439921) (Pb). Among men, reported occupational exposures to aluminum (7429905), manganese (7439965), magnesium (7439954), nickel (7440020), selenium (7782492), Pb and mercury (7439976) were not correlated significantly with the occurrence of the disease. There were no differences between patients and comparisons as to their history of immunization, thyroid and mineral disorders, travel history, history of paralytic poliomyelitis and fractures. The authors conclude that occupational heavy metal exposures are not a likely etiological factor in the occurrence of amyotrophic lateral sclerosis.

8
AU - Halliwell B
TI - Manganese ions, oxidation reactions and the superoxide radical.
UI - 84192176/BACK83
AB - The variable valency of the transition element manganese allows it to catalyse redox reactions. This can be made use of in mangano -superoxide dismutase enzymes, but manganese-induced oxidation of NADH and dihydroxyflumarates generate damaging oxygen radicals. Manganese-stimulated oxidations of adrenalin and its derivatives to form toxic products may be involved in the etiology of manganese neurotoxicity.
SO - Neurotoxicology 1984 Spring;5(1):113-7

20
AU - HAMS GA
AU - FABRI JK
TI - AN ANALYSIS FOR BLOOD MANGANESE USED TO ASSESS ENVIRONMENTAL EXPOSURE
SI - BIOSIS/88/25205/TOXLINE
SO - CLIN CHEM; 34 (6). 1988. 1121-1123.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN GRAPHITE-FURNACE ATOMIC ABSORPTION SPECTROMETRY NEUROTOXICITY AUSTRALIAN ABORIGINES

23
AU - Heilbronn E
AU - Eriksson H
AU - Haeggblad J
TI - Neurotoxic effects of manganese: studies on cell cultures, tissue homogenates and intact animals
SI - CA/098/192715E/TOXLIT
SO - Neurobehav. Toxicol. Teratol.; VOL 4, ISS 6, 1982,655-8
AB - CBAC COPYRIGHT: CHEM ABS A review and discussion with 27 refs. Review manganese neurotoxicity Cell culture manganese review Animal manganese review Tissue manganese review

6

AU - Huang C-C
AU - Chu N-S
AU - Lu C-S
AU - Wang J-D
AU - Tsai J-L
AU - Tzeng J-L
AU - Wolters EC
AU - Calne DB
TI - Chronic Manganese Intoxication
SI - NIOSH/00191770/TOXLINE
SO - Archives of Neurology, Vol. 46, No. 10, pages 1104-1106, 23 references, 1989
AB - Chronic manganese (7439965) poisoning occurring in six metal workers was described. The workers were male, 38 to 47 years old, and worked in the smelting department of a ferromanganese alloy factory in Taiwan. Clinical, neurological, and neuropsychological examinations showed bradykinesia characterized by a masked face, blinking, clumsiness with impaired dexterity, gait abnormalities, and rigidity. Five patients had hypophonia. Three had a mild, low amplitude tremor and micrographia and suffered from insomnia and impotence. Personality changes were noted in only one patient. Electroencephalographic, electromyographic, nerve conduction velocity parameters, and evoked potentials were within the normal range for all patients. Performance on facial recognition and visual constructive praxis tests was impaired. All hematological and serum and urine chemistry parameters were normal. Manganese concentrations in the blood, scalp, and pubic hair were significantly elevated, ranging from three to 300 times the normal values. Industrial hygiene sampling showed airborne manganese concentrations ranging up to 28mg/m3. The highest concentrations occurred near the smelting furnace. All patients had worked for at least 2 years in the vicinity of the furnace without using any protective equipment. The patients were treated with levodopa and carbidopa daily for 8 weeks. Three were also given EDTA for 8 weeks. Treatment with levodopa and carbidopa resulted in considerable improvement in the patients' symptoms; however, performance on the facial recognition and visual constructive tests were not improved. EDTA had no therapeutic value. The authors conclude that chronic manganese poisoning produces symptoms that resemble Parkinson's disease. The response to levodopa and carbidopa should be confirmed in additional studies.

3
AU - Hussain T
AU - Ali MM
AU - Chandra SV
TI - The combined effect of Pb2+ and Mn2+ on monoamine uptake and Na+, K+-ATPase in striatal synaptosomes.
UI - 87309564/BACK86
AB - Rat striatal synaptosomes (P2-fraction) were subjected to lipoperoxidation by the addition of 120 microM Fe2+ and 200

microM ascorbic acid. This preparation (pretreated synaptosomes) was used to investigate the interaction of Pb2+ and Mn2+ on the uptake of tritiated catecholamines, Na+, K+-ATPase activity and malondialdehyde (MDA) formation in order to understand the mechanism of enhanced neurotoxicity by concurrent exposure to these metals. The combination of Pb2+ and Mn2+ (25 microM + 100 microM, respectively) produced a significant increase in the uptake of 3H-Dopamine only in the untreated synaptosomes. No significant effect was noted on the uptake of 3H-Norepinephrine in either pretreated or untreated synaptosomes. However, the combination of Pb2+ and Mn2+ produced a pronounced decrease in the activity of Na+, K+-ATPase, but the magnitude of the change was the sum of the individual metal effects. Metal interaction did not produce any significant change in the formation of MDA compared to the control (without addition of metals). These results indicate that Pb2+ and Mn2+ interaction may produce inhibition in the activity of transport ATPase in both the preparation of synaptosomes, with more pronounced effect of synaptosomes subjected to lipoperoxidation and these changes may be responsible for the disruption in the physiology of nerve impulse transmission.

SO - J Appl Toxicol 1987 Aug;7(4):277-80

26
AU - HUSSAIN T
AU - ALI MM
AU - CHANDRA SV
TI - THE COMBINED EFFECT OF LEAD AND MANGANESE ON MONOAMINE UPTAKE AND SODIUM POTASSIUM ATPASE IN STRIATAL SYNAPTOSOMES
SI - BIOSIS/87/31524/TOXLINE
SO - J APPL TOXICOL; 7 (4). 1987. 277-280.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM RAT DOPAMINE SYNERGISM LIPOPEROXIDATION NEUROTOXICITY

23
AU - KIHIRA T
TI - MORPHOLOGICAL MORPHOMETRICAL AND METAL ANALYTICAL STUDIES OF ORAL ALUMINUM NEUROTOXICITY
SI - BIOSIS/87/34882/TOXLINE
SO - BRAIN NERVE (TOKYO); 39 (7). 1987. 633-641.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM RABBIT CALCIUM MAGNESIUM MANGANESE AMYOTROPHIC LATERAL SCLEROSIS AXONAL SWELLING SPHEROID ENVIRONMENTAL FACTOR

14
AU - Kontur PJ
AU - Fechter LD
TI - Brain manganese, catecholamine turnover, and the development of startle in rats prenatally exposed to manganese
SI - CA/103/083018F/TOXLIT
SO - Teratology; VOL 32, ISS 1, 1985,1-11
AB - CBAC COPYRIGHT: CHEM ABS Maternal-fetal Mn transfer and the

susceptibility of prenatal animals to Mn neurotoxicity were examd. This was approached by studying the ability of Mn to cross the placenta and reach the fetal central nervous system using radiotracer and at. absorption spectroscopy techniques. Mn is thought to disrupt catecholamine neurotransmission in the central nervous system. This was examd. in newborn rats by alpha-methyl-p-tyrosine-induced catecholamine turnover and the development of the acoustic startle response. The results suggest that there are limits on fetal Mn accumulation under conditions of both normal and excessive dietary Mn levels. Mn accumulation in the fetal brain after exposure to increased dietary Mn does not alter either dopamine [51-61-6] or norepinephrine [51-41-2] turnover or the development of the acoustic startle response. Excess Mn does not appear to be neurotoxic to fetal rats in spite of its limited accumulation in nervous tissue after gestational exposure.

3
AU - Kontur PJ
AU - Fechter LD
TI - Brain manganese, catecholamine turnover, and the development of startle in rats prenatally exposed to manganese.
UI - 85301073/BACK83
AB - Manganese (Mn) can be neurotoxic when present in high concentrations. Neonatal animals show differential absorption, accumulation, and excretion of Mn relative to adults. If similar kinetic differences exist during gestation, then fetal animals may be susceptible to Mn neurotoxicity. The objective of this study was to examine maternal-fetal Mn transfer and the susceptibility of prenatal animals to Mn neurotoxicity. This was approached by studying the ability of Mn to cross the placenta and reach the fetal central nervous system using radiotracer and atomic absorption spectroscopy techniques. Manganese is thought to disrupt catecholamine neurotransmission in the central nervous system. This was examined in newborn rats by alpha-methyl-para-tyrosine induced catecholamine turnover and the development of the acoustic startle response. The results suggest that there are limits on fetal Mn accumulation under conditions of both normal and excessive dietary Mn levels. Manganese accumulation in the fetal brain after exposure to increased dietary Mn does not alter either dopamine or norepinephrine turnover or the development of the acoustic startle response. Excess Mn does not appear to be neurotoxic to fetal rats in spite of its limited accumulation in nervous tissue after gestational exposure.
SO - Teratology 1985 Aug;32(1):1-11

3
AU - Krigman MR
TI - Neuropathology of Heavy Metal Intoxication
SI - NIOSH/00169819/TOXLINE65
SO - Environmental Health Perspectives, Vol. 26, pages 117-120, 21

references, 19781978
AB - The pathology of heavy metal neurotoxicity in man was discussed. Lead (7439921) affected both the central and peripheral nervous systems of man. The neuropathy was characterized by a loss of nerve fibers and to some degree segmental demyelination. Gray and white matter lesions and neuronal necrosis were variable. When necrosis was present, it was usually in neocortex and might be the result of the vasculopathy and anoxia. Astrocytes and microglia were in an activated state. Seizures and coma were reported in the absence of pathologic changes. Cadmium (7440439) poisoning induced no neurotoxic effects. Arsenic (7440382) compounds might produce an acute encephalopathy, and chronic exposure could result in a neuropathy, characterized by axon and myelin degeneration. Of mercury (7439976) compounds, alkylmercury and inorganic mercury compounds produced a degeneration in the central and peripheral nervous systems. The intoxication was cumulative. A minimal level was required to initiate degeneration. The changes in the central nervous system involved the cerebellum, cerebral cortex, and basal ganglia. The peripheral neuropathy was characterized by axon and myelin degeneration. Manganese (7439965) toxicity affected the basal ganglia and to some degree the cerebellum. Biochemical lesions were present where there was evidence of heavy metal burdens without discernible pathologic changes. A quantitative or morphometric analysis might be more revealing in these cases because of changes in the numbers or proportions of critical elements. The morphometric analysis demonstrated distinct differences between lead toxicity and undernutrition in suckling rats. Morphometric studies are necessary for demonstrating and defining the subtle burdens of toxicants and determining the full range of their effects.

62
AU - Kristensson K
AU - Eriksson H
AU - Lundh B
AU - Plantin L-O
AU - Wachtmeister L
AU - el Azazi M
AU - Morath C
AU - Heilbronn E
TI - Effects of Manganese Chloride on the Rat Developing Nervous System
SI - NIOSH/00164988/TOXLINE
SO - Acta Pharmacologica et Toxicologica, Vol. 59, No. 5, pages 345-348, 13 references, 19861986
AB - Studies were performed on Sprague-Dawley-rats during postnatal development to examine the effect of manganese-chloride (7773015) on nervous system maturation and on its monoamines and their metabolites. Rats received daily doses of 150mg/kg manganese (7439965) by gastric intubation, and were examined up to 44 days of age. Some rats were exposed until the age of 15 days, and

killed at 60 days of age. In 15 and 20 day old rats, no morphological alterations or signs of disturbances in nervous system maturation were detected, despite high brain levels of manganese. Normal axonal growth and myelination, development of dendritic trees, and synaptogenesis were observed. Transient motor effects, manifested at 15 to 22 days of age, could be explained by biochemical effects. Various metabolites were studied, but only homovanillic-acid (HVA) content was altered by treatment with manganese; changes were not caused by an effect on catechol-O-methyl-transferase activity. When manganese exposure was stopped at the age of 15 days, HVA depression was not observed at 60 days, indicating reversibility. Findings indicate that divalent manganese is not highly toxic for the developing nervous system at this exposure length.

1
AU - LAI J CK
AU - GUEST JF
AU - LEUNG T KC
AU - LIM L
AU - DAVISON AN
TI - The effects of cadmium, manganese and aluminum on sodium-potassium-activated ATPase (EC 3.6.1.3) and magnesium-activated ATPase activity and choline uptake in rat brain synaptosomes.
SI - HEEP/80/07838/TOXLINE65
SO - BIOCHEM PHARMACOL; 29 (2). 1980. 141-146.
AB - HEEP COPYRIGHT: BIOL ABS. The effects of Cd2+, Mn2+ and Al3+ on rat brain synaptosomal Na-K-ATPase and Mg-ATPase activity and choline uptake were studied. All 3 types of metal ions inhibited Na-K-ATPase activity more markedly than Mg-ATPase activity. The rank order of inhibition of Na-K-ATPase was: Cd2+ (IC50 (50% inhibition concentration) = 5.4 muM) > Mn2+ (IC50 = 955 muM)ase was: Cd2+ (IC50 = 316 muM) > Mn2+ (IC50 = 5.5 mM) > Al3+ (IC50 = 21.9 mM). Al3+ was most potent in inhibiting synaptosomal choline uptake (IC50 = 24 muM in the absence of Ca2+ and 123 muM in the presence of 1 mM Ca2+) Cd2+ (IC50 = 363 muM) was a more effective inhibitor of choline uptake than Mn2+ (IC50 = 1.2-1.5 mM). The presence of 1 mM Ca2+ did not alter choline uptake, nor did it antagonize the inhibitory actions of the 3 metals. The observations that Cd2+ and Al3+ inhibited synaptosomal choline uptake, but did not show parallel inhibitory effects on Na-K-ATPase activity directly contradicts the ionic gradient hypothesis. These results are also discussed in relation to the in vivo neurotoxicity of Cd, Mn and Al.

5
AU - Lai JC K
AU - Leung TK C
AU - Whatley SA
AU - Lim L
TI - Neurotoxic effects of manganese, cadmium and lithium ions on

astrocytes and neurons in primary culture
SI - CA/109/018433X/TOXLIT
SO - Neurol. Neurobiol.; VOL 39, ISS Biochem. Pathol. Astrocytes, 1988,233-4
AB - CBAC COPYRIGHT: CHEM ABS Of the 3 title metals, Cd was most toxic, and in primary cultures of astrocytes and mixed cultures of neurons on an astroglia monolayer it decreased the activities of all the investigated enzymes. The primary cultures of astrocytes and mixed cultures of neurons on astrocytes are excellent in vitro model systems for the study of transmitter and metabolic mechanisms underlying the neurotoxicity of these metals; Mn2+, Cd2+, and Li+ exert differential metabolic and cytotoxic effects on astrocytes and neurons in primary culture.

41
AU - LAI J CK
AU - BAKER A
AU - CARLSON K C JR
AU - BLASS JP
TI - DIFFERENTIAL EFFECTS OF MONOVALENT DIVALENT AND TRIVALENT METAL IONS ON RAT BRAIN HEXOKINASE EC-2.7.1.1
SI - BIOSIS/85/06649/TOXLINE
SO - COMP BIOCHEM PHYSIOL C COMP PHARMACOL TOXICOL; 80 (2). 1985. 291-294.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM CHROMIUM COPPER CALCIUM STRONTIUM BARIUM ZINC CADMIUM MERCURY LEAD MANGANESE IRON COBALT NICKEL ALUMINUM NEUROTOXICITY POLLUTION

1
AU - Lai JC K
AU - Guest JF
AU - Leung TK C
AU - Lim L
AU - Davison AN
TI - The effects of cadmium, manganese, and aluminum on sodium-potassium-activated and magnesium-activated adenosine triphosphatase activity and choline uptake in rat brain synaptosomes
SI - CA/093/001341U/TOXLIT65
SO - Biochem. Pharmacol.; VOL 29, ISS 2, 1980,141-6
AB - CBAC COPYRIGHT: CHEM ABS Cd, Mn, and Al all inhibited Na,K-activated ATPase (EC 3.6.1.3) more than Mg-activated ATPase of rat brain synaptosomes. (9000-83-3 ATPase) The IC50 values for Cd, Mn, and Al were 5.4 and 955 muM and 8.3 mM, resp, for Na,K-ATPase, and similarly 316 muM and 5.5 and 21.9 mM, resp. for Mg-ATPase. Al was most potent in inhibiting synaptosomal choline uptake, IC50 24 and 123 muM in the absence and presence of Ca (1mM), resp. (62-49-7 Choline) Cd was more effective than Mn (IC50 values 363 muM and 1.2-1.5 mM, resp.). The presence of Ca did not alter choline uptake or antagonize the inhibitory actions of the 3 metals. Since Cd and Al inhibit synaptosomal choline uptake but do not show parallel inhibitory effects on

IV-D-56

KOLBYE ASSOCIATES
7313 HELMSDALE ROAD
BETHESDA, MARYLAND 20817

UI - 83102540/BACK72
AU - Donaldson J
AU - McGregor D
AU - LaBella F
TI - Manganese neurotoxicity: a model for free radical mediated neurodegeneration?
UI - 82104577/BACK80
AB - In man, manganese neurointoxication is characterised in the early phase by behavior reminiscent of that observed in schizophrenia. During chronic manganese intoxication the neuropsychiatric symptoms manifested earlier disappear and are followed by a permanent neurological phase typified by extrapyramidal symptoms similar to those of Parkinson's disease. Study of manganese intoxication in animals may provide important clues towards elucidation of the biochemical defect underlying neuropsychiatric as well as extrapyramidal disease. Investigations in our laboratory suggest that neurotoxicity of manganese is an exaggeration of function in normal neuronal homeostasis. Manganese neurointoxication in neonatal rats resulted in significant depression of lipid peroxidation in several rat brain regions examined. In the striatum, lipid peroxidative activity was abolished, an effect which may be related to alteration in neurotransmitters often observed in the striatum of manganese treated rats. The chronic, extrapyramidal stage of manganism, may ensue when excess Mn2+ is oxidised to higher valency forms where it can potentiate the autoxidation of catecholamines, like dopamine, resulting in concomitant formation of free radicals and cytotoxic quinones. This latter effect may arise preferentially in the substantia nigra, where neuromelanin is formed nonenzymatically by autoxidation of dopamine.
SO - Can J Physiol Pharmacol 1982 Nov;60(11):1398-405

8
AU - ALESSIO L
AU - APOSTOLI P
AU - FERIOLI A
AU - LOMBARDI S
TI - INTERFERENCE OF MANGANESE ON NEUROENDOCRINAL SYSTEM IN EXPOSED WORKERS PRELIMINARY REPORT
SI - BIOSIS/90/05069/TOXLINE
SO - FIRST INTERNATIONAL MEETING ON MOLECULAR MECHANISMS OF METAL TOXICITY AND CARCINOGENICITY, URBINO, ITALY, SEPTEMBER 19-22, 1988. BIOL TRACE ELEM RES; 21 (0). 1989. 249-254.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN DOPAMINERGIC CONTROL NEUROTOXICITY

2
AU - Ali MM
AU - Murthy RC
AU - Mandal SK
AU - Chandra SV

TI - Effect of low protein diet on manganese neurotoxicity: III. Brain neurotransmitter levels.
UI - 86092419/BACK83
AB - The effect of concurrent low protein (10% casein) diet and manganese (Mn) exposure (3 mg/ml drinking water) on brain levels of dopamine (DA), norepinephrine (NE) and 5-hydroxytryptamine (5-HT) were investigated in Fo-growing (90 days exposure), Fo-diet rehabilitated (low----normal protein diet-28 days) and F1-weaned rats. Mn exposure in either diet group resulted in a significant increase in the DA and NE levels but a decrease in the 5-HT level. These effects were more pronounced in the rats fed the low protein diet, especially in the F1-offsprings. Diet rehabilitation reduced the effects of Mn exposure.
SO - Neurobehav Toxicol Teratol 1985 Sep-Oct;7(5):427-31

34
AU - ALI MM
AU - MURTHY RC
AU - MANDAL SK
AU - CHANDRA SV
TI - EFFECT OF LOW PROTEIN DIET ON MANGANESE NEUROTOXICITY III. BRAIN NEUROTRANSMITTER LEVELS
SI - BIOSIS/86/08004/TOXLINE
SO - NEUROBEHAV TOXICOL TERATOL; 7 (5). 1985. 427-432.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM RAT DOPAMINE NOREPINEPHRINE 5 HYDROXYTRYPTAMINE

21
AU - Ali MM
AU - Murthy RC
AU - Saxena DK
AU - Chandra SV
TI - Effect of low-protein diet on manganese neurotoxicity: II. Brain GABA and seizure susceptibility
SI - CA/099/065503E/TOXLIT
SO - Neurobehav. Toxicol. Teratol.; VOL 5, ISS 3, 1983,385-9
AB - CBAC COPYRIGHT: CHEM ABS The effects of Mn (3 mg/mL in drinking water) on brain GABA [56-12-2] content and electroshock seizure susceptibility in low (10% casein) and normal (21% casein) protein-fed rats were investigated. Mn exposure decreased brain GABA, lowered the seizure threshold, and increased the seizure duration. These effects were more marked in the low protein-fed rats. Diet rehabilitation caused a recovery in the GABA levels but had only a moderating effect on the seizure susceptibility and duration. There was an inverse correlation between the brain GABA levels and seizure threshold. Results indicated a lowered GABAergic activity and a functional dysbalance between the GABAergic-dopaminergic neuronal systems in Mn toxicity.

12
AU - Ali MM
AU - Murthy RC

AU - Saxena DK
AU - Srivastava RS
AU - Chandra SV
TI - Effect of low protein diet on manganese neurotoxicity: I. Developmental and biochemical changes.
UI - 83271721/BACK80
AB - The first in a series of studies on the effect of concurrent low protein diet (10% casein) and manganese exposure (Mn2+, 3 mg/ml drinking water) in rats is reported here. The effect on growing (Fo-90 days) rehabilitated (Fo low leads to normal protein diet-28 days) and the F1 generation pups (weaned) were studied. Mn2+ exposure had no significant effect on growth pattern, brain weight or brain and plasma protein contents in either dietary groups. The diet regimen had no significant effect on the accumulation of Mn2+ in brain in any of the groups studied but the levels were higher in the F1 pups than in the parent (Fo) generation. In the F1 pups Mn2+ exposure had no effect on eye opening in either dietary group, delayed the development of startle reflex in low protein fed group only but the air righting reflex development was delayed in both the dietary groups, the effect being more marked in the low protein fed group. These changes reflect the early neurotoxic effect of Mn2+.
SO - Neurobehav Toxicol Teratol 1983 May-Jun;5(3):377-83

22
AU - Ali MM
AU - Murthy RC
AU - Saxena DK
AU - Srivastava RS
AU - Chandra SV
TI - Effect of low-protein diet on manganese neurotoxicity: I. Developmental and biochemical changes
SI - CA/099/048678Y/TOXLIT
SO - Neurobehav. Toxicol. Teratol.; VOL 5, ISS 3, 1983,377-83
AB - CBAC COPYRIGHT: CHEM ABS The effect of concurrent low-protein diet (10% casein) and Mn exposure (3 mg/mL drinking water) in rats was investigated. The effect on growing, dietary-rehabilitated, and weaned rats was studied. Mn exposure had no significant effect on growth pattern, brain wt., or brain and plasma protein contents in either dietary group. The diet regimen had no significant effect on the accumulation of Mn in the brain in any of the groups studied but the levels were higher in the F1 pups than in the parent (Fo) generation. In the F1 pups, Mn exposure had no effect on eye opening in either dietary group, delayed the development of startle reflex in the low protein-fed group only but the air righting reflex development was delayed in both the dietary groups, the effect being more marked in the low protein-fed group. These changes reflect the early neurotoxic effect of Mn.

11
AU - Ali MM

AU - Murthy RC
AU - Saxena DK
AU - Chandra SV
TI - Effect of low protein diet on manganese neurotoxicity: II. Brain GABA and seizure susceptibility.
UI - 83271722/BACK83
AB - The effect of manganese (Mn2+, 3 mg/ml drinking water) on brain GABA content and electroshock seizure susceptibility in low (10% casein) and normal (21% casein) protein fed rats were investigated. Manganese exposure caused a decrease in the brain GABA content, lowered the seizure threshold and increased the seizure duration. These effects were more marked in the low protein fed rats. Diet rehabilitation caused a recovery in the GABA levels but has only a moderating effect on the seizure susceptibility and duration. An inverse correlation was observed between the brain GABA levels and seizure threshold. Results indicate a lowered GABA-ergic activity and a functional dysbalance between the GABA-ergic-dopaminergic neuronal systems in manganese toxicity.
SO - Neurobehav Toxicol Teratol 1983 May-Jun;5(3):385-9

57
AU - Anonymous
TI - Diseases Caused by Manganese and Its Toxic Compounds
SI - NIOSH/00171741/TOXLINE
SO - Early Detection of Occupational Diseases, World Health Organization, Geneva, pages 69-73, 19861986
AB - Occupational diseases from exposure to manganese (7439965) and manganese compounds were discussed. The authors indicate that exposure to manganese and its oxides, carbonates, and silicates, can occur during the production of dry cell batteries, in the production of potassium-permanganate (7722647), in the electrode coating of welding rods, in drying linseed-oil, in bleaching of glass and textiles, dyeing and tanning of leather, and the manufacture of fertilizers. Organic carbonyls of manganese are found in fuel oil, smoke inhibitors, and as antiknock additives in gasoline. Following inhalation, only those particles which are small enough to reach the alveoli are absorbed, after which most manganese is redistributed to the liver. Acute poisoning is rare. Long term exposure damages the central nervous system and lungs. Damage to the central nervous system is first manifested by impaired mental capacity and usually appears only after exposures of 2 or more years. Manganese exposure seems to decrease the immunological resistance to respiratory bacterial or viral infections. Other effects include decreased blood pressure, dysproteinemia, and reproductive disturbances. Pregnant women may suffer an abortion following exposure. The authors conclude that persons with psychic or neurological disorders should not work with manganese. The suppression of dust and fumes would help control exposure levels. Dry drilling in mines should be replaced by wet drilling. Respiratory protective equipment should be used.

Na,K-ATPase, the ionic gradient hypothesis is contradicted. In vivo neurotoxicity of Cd, Mn, and Al is also discussed.

27
AU - LAUWERYS R
AU - BUCHET JP
AU - ROELS H
AU - BERNARD A
AU - GENNART JP
TI - BIOLOGICAL ASPECTS OF OCCUPATIONAL EXPOSURE TO CADMIUM AND TO SOME OTHER METALS
SI - BIOSIS/87/21362/TOXLINE
SO - SYMPOSIUM ON EPIDEMIOLOGY AND OCCUPATIONAL RISKS HELD AT THE 11TH MEETING OF THE ASSOCIATION DES EPIDEMIOLOGISTES DE LANGUE FRANCAISE (FRENCH LANGUAGE ASSOCIATION OF EPIDEMIOLOGISTS), NANCY, FRANCE, MARCH 3-4, 1986. REV EPIDEMIOL SANTE PUBLIQUE; 34 (4-5). 1986 (RECD. 1987). 280-285.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN MERCURY MANGANESE ARSENIC NEPHROTOXICITY NEUROTOXICITY PSYCHOMOTOR TOXICITY

54
AU - Liccione JJ
AU - Maines MD
TI - Selective Vulnerability of Glutathione Metabolism and Cellular Defense Mechanisms in Rat Striatum to Manganese
SI - NIOSH/00183977/TOXLINE
SO - Journal of Pharmacology and Experimental Therapeutics, Vol. 247, No. 1, pages 156-161, 39 references, 19881988
AB - The effects of manganese (7439965) on whole brain and striatal glutathione (GSH) metabolism and cellular defense mechanisms were studied in rats. Adult male Sprague-Dawley-rats were administered 1750 micromoles per kilogram manganous-chloride (7773015) over a 7 day period by subcutaneously implanted osmotic minipumps. They were killed at the end of the dosing period, the brains were removed, and the striatum was dissected out. Whole brain and striatal homogenates and the mitochondrial, microsomal, and cytosolic fractions were prepared and assayed for catalase, glutathione-peroxidase (GSHPx), oxidized-glutathione-reductase (GSSG-red), gamma-glutamyl-transpeptidase (GGT), gamma-glutamylcysteine-synthetase (GGTcyase), GSH, dopamine, 3,4-dihydroxyphenylacetic-acid (DHPAA), 4-hydroxy-3-methylphenylacetic-acid (OHMePAA), and manganese. Manganous-chloride significantly reduced the concentrations of dopamine, DHPAA, and OHMePAA in the striatum. The manganese contents of the mitochondrial fraction of the whole brain and striatum were significantly increased. Manganese significantly reduced whole brain and striatal cytosolic and mitochondrial GSHPx activity, the greatest reduction occurring in the striatal mitochondria. Catalase activity was decreased only in the striatum. Striatal GSH content was reduced sharply; however, whole brain GSH was reduced only slightly. Manganese increased whole brain and striatal GGT activity and decreased whole brain

and striatal GSSG-red activity. The increases in GGT activity were similar in both the whole brain and striatum, whereas the decrease in GSSG-red was greater in the striatum. GGTcyase activity was not significantly affected by manganese. The authors conclude that the cellular defense mechanisms of certain enzymes important in GSH metabolism are significantly altered by manganese in the brain of rats, especially in the striatum. These changes may be involved in manganese neurotoxicity.

5
AU - Liccione JJ
AU - Maines MD
TI - Selective vulnerability of glutathione metabolism and cellular defense mechanisms in rat striatum to manganese.
AD - Department of Biophysics, University of Rochester School of Medicine, New York.
UI - 89011450/MEDLINE
AB - The present findings provide experimental evidence for the hypothesis that compromised cellular defense mechanisms, i.e., glutathione (GSH), GSH-peroxidase and catalase in the brain may be involved in neuronal degeneration caused by manganese (Mn) neurotoxicity. Moreover, data are presented demonstrating that the striatum is particularly susceptible to the deleterious effects of Mn. Specifically, exposure to subchronic MnCl2 produced significant reductions in GSH-peroxidase activity in the cytosol and mitochondrial fractions of the whole brain and the striatum. The decrease in GSH-peroxidase was most pronounced in the mitochondrial fraction of the striatum where the activity was reduced to 35% of the control. Catalase activity was also decreased in the striatum of rats treated with Mn but not in the whole brain. GSH content was markedly depleted (20% of the control) in the striatum, although only modestly decreased in whole brain (80% of the control). The alterations in the above parameters were accompanied by depletion of dopamine and dopamine metabolites in the striatum. The treatment of rats with Mn also decreased the activity of oxidized glutathione-reductase; the same treatment increased the activity of gamma-glutamyltranspeptidase. The activity of gamma-glutamylcysteine synthetase was not altered by Mn. The possible relevancy of the findings of this study to understanding the mechanism of Mn neurotoxicity of dopamine systems is discussed.
SO - J Pharmacol Exp Ther 1988 Oct;247(1):156-61

51
AU - Liccione JJ
AU - Maines MD
TI - Manganese-Mediated Increase in the Rat Brain Mitochondrial Cytochrome P-450 and Drug Metabolism Activity: Susceptibility of the Striatum
SI - NIOSH/00186674/TOXLINE
SO - Journal of Pharmacology and Experimental Therapeutics, Vol. 248,

No. 1, pages 222-228, 37 references, 19891989

AB - The response of the cytochrome-P-450 levels and drug hydroxylation activities in the brain microsomal and the mitochondrial fractions to in-vivo manganese (7439965) (Mn) treatment were explored. Mn treatment of male Sprague-Dawley-rats for 7 days caused approximately 2.5 and 1.6 fold increases in the hemoprotein content in the mitochondrial and microsomal fractions of whole brain, respectively. Significant increases in the hydroxylation of benzo(a)pyrene and D-amphetamine were noted in both mitochondrial and microsomal fractions of striatum. Hydroxylation activities were increased two to three fold in the mitochondrial fraction. The NADH dependent hydroxylation of both substrates by the mitochondrial fraction was effectively inhibited by SKF-525A treatment. The striatal mitochondrial metabolism of D-amphetamine was increased by more than two fold in rats treated with Mn while in whole brain the activity showed only a 25 percent increase. Amphetamine hydroxylation activity of the striatal mitochondria exceeded that of whole brain by 1.75 fold. Striatal microsomal amphetamine hydroxylation was increased only 33 percent; whole brain microsomes showed similar levels of activity. Measurement of respiratory cytochromes showed that Mn treatment decreased the concentrations of cytochrome-b, cytochrome-c1, cytochrome-c, and cytochrome-a. A marked decrease in gamma-aminolevulinate-synthetase was also noted. In the microsomal fraction, Mn treatment modestly increased the total heme concentration and modestly decreased heme oxygenase activity. The authors suggested that the increases in the microsomal and mitochondrial cytochrome-P-450 may reflect intrinsic properties of cytochrome-P-450 isozymes in these organelles, including their turnover rate, preferential utilization of heme and/or susceptibility to degradation. Possible relevance of these findings to the manganese neurotoxicity of dopamine pathways is considered.

4

AU - Liccione JJ

AU - Maines MD

TI - Selective vulnerability of glutathione metabolism and cellular defense mechanisms in rat striatum to manganese

SI - CA/109/224229P/TOXLIT

SO - J. Pharmacol. Exp. Ther.; VOL 247, ISS 1, 1988,156-61

AB - CBAC COPYRIGHT: CHEM ABS The present findings provide exptl. evidence for the hypothesis that compromized cellular defense mechanisms, i.e., GSH peroxidase and catalase in the brain may be involved in neuronal degeneration caused by Mn neurotoxicity. Moreover, data are presented demonstrating that the striatum is particularly susceptible to the deleterious effects of Mn. Specifically, exposure to subchronic MnCl2 produced significant redns. in GSH peroxidase activity in the cytosol and mitochondrial fractions of the whole brain and the striatum. The decrease in GSH peroxidase was most pronounced in the

mitochondrial fraction of the striatum where the activity was reduced to 35% of the control. Catalase activity was also decreased in the striatum of rats treated with Mn but not in the whole brain. GSH content was markedly depleted (20% of the control) in the striatum, although only modestly decreased in whole brain (80% of the control). The alterations in the above parameters were accompanied by depletion of dopamine and dopamine metabolites in the striatum. The treatment of rats with Mn also decreased the activity of oxidized glutathione reductase; the same treatment increased the activity of gamma-glutamyltranspeptidase. The activity of gamma-glutamylcysteine synthetase was not altered by Mn. The possible relevancy of the findings of this study to understanding the mechanism of Mn neurotoxicity of dopamine systems is discussed.

15
AU - LICCIONE JJ
AU - MAINES D
TI - SELECTIVE VULNERABILITY OF GLUTATHIONE METABOLISM AND CELLULAR DEFENSE MECHANISMS IN RAT STRIATUM TO MANGANESE
SI - BIOSIS/89/01662/TOXLINE
SO - J PHARMACOL EXP THER; 247 (1). 1988. 156-161.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM NEUROTOXICITY MANGANISM MANGANESE POISONING DOPAMINE DEFICIENCY

2
AU - Liccione JJ
AU - Maines MD
TI - Manganese-mediated increase in the rat brain mitochondrial cytochrome P-450 and drug metabolism activity: susceptibility of the striatum
SI - CA/110/226730Q/TOXLIT
SO - J. Pharmacol. Exp. Ther.; VOL 248, ISS 1, 1989,222-8
AB - CBAC COPYRIGHT: CHEM ABS The present study describes the high degree of sensitivity of the mitochondrial fraction of the striatum to Mn2+-mediated perturbations in mixed-function oxidase activity. This study also defines the brain mitochondrial cytochrome P 450 subject to increase by Mn2+. In the striatum of Mn2+-treated animals (7 days), hydroxylation of benzo[a]pyrene and D-amphetamine was significantly increased in both the mitochondrial and the microsomal fractions. The effects were more pronounced in the mitochondrial fraction where hydroxylation activities were increased by 2- to 3-fold. SKF-525A effectively inhibited NADH-dependent hydroxylation of both substrates by the mitochondrial fraction. In the Mn2+-treated animals, significant increases in mitochondrial and microsomal cytochrome P 450 concn. were also noted. In the mitochondria, the hemoprotein concn. was increased by nearly 2.5-fold; in the microsomes, the concn. of the cytochrome was increased by about 1.6-fold. Mn2+ appeared to selectively increase cytochrome P 450 concn. since that of other cytochromes including the mitochondrial b, c1, c, and a, and the

microsomal cytochrome b5 was not increased. In addn., the activity of mitochondrial delta-aminolevulinate synthetase was not increased and that of the microsomal heme oxygenase was inhibited by Mn2+ treatment. Apparently, the increases in the microsomal and the mitochondrial cytochrome P 450 may reflect intrinsic properties of cytochrome P 450 isoenzymes in these organelles, including their turnover rate, preferential utilization of heme and/or susceptibility to degrdn. The possible relevance of the findings of Mn2+ neurotoxicity of dopamine pathways is discussed.

4
AU - Liccione JJ
AU - Maines MD
TI - Manganese-mediated increase in the rat brain mitochondrial cytochrome P-450 and drug metabolism activity: susceptibility of the striatum.
AD - Department of Biophysics, University of Rochester School of Medicine, New York.
UI - 89110795/MEDLINE
AB - The present study describes the high degree of sensitivity of the mitochondrial fraction of the striatum to Mn++-mediated perturbations in mixed-function oxidase activity. This study also defines the brain mitochondrial cytochrome P-450 subject to increase by Mn++. In the striatum of Mn++-treated animals (7 days) hydroxylation of benzo(a)pyrene and D-amphetamine was significantly increased in both the mitochondrial and the microsomal fractions. The effects were more pronounced in the mitochondrial fraction where hydroxylation activities were increased by 2- to 3-fold. SKF-525A (2-diethylaminoethyl-2,2-di-phenylvalerate hydrochloride) effectively inhibited NADH-dependent hydroxylation of both substrates by the mitochondrial fraction. In the Mn++-treated animals, significant increases in mitochondrial and microsomal cytochrome P-450 concentration were also noted. In the mitochondria, the hemoprotein concentration was increased by nearly 2.5-fold; in the microsomes the concentration of the cytochrome was increased by about 1.6-fold. Mn++ appeared to selectively increase cytochrome P-450 concentration since that of other cytochromes including the mitochondrial b, c1, c and a, and the microsomal cytochrome b5 was not increased. In addition, the activity of mitochondrial delta-aminolevulinate synthetase was not increased and that of the microsomal heme oxygenase was inhibited by Mn++ treatment. It is suggested that increases in the microsomal and the mitochondrial cytochrome P-450 may reflect intrinsic properties of cytochrome P-450 isozymes in these organelles, including their turnover rate, preferential utilization of heme and/or susceptibility to degradation. The possible relevance of the findings to Mn++ neurotoxicity of dopamine pathways is discussed.
SO - J Pharmacol Exp Ther 1989 Jan;248(1):222-8

16
AU - LONDON R
TI - Magnetic resonance imaging studies of heavy metal distribution
SI - CRISP/90/S50112-02/TOXLINE
SA - U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
SO - Crisp Data Base National Institutes Of Health
AB - RPROJ/CRISP It has recently become possible to obtain spatially resolved "images" of the nuclear spins of biological and chemical materials. Magnetic resonance imaging or "MRI" is rapidly evolving into an important diagnostic tool for a wide range of human pathologies. Such imaging studies have been almost exclusively limited to the detection of protons, which in turn provide images of the abundant protonated molecules in biological tissues: fat and water. Since image intensity is dependent on the density of protons in a given sample volume, as well as on the nuclear relaxation properties of these protons, it becomes possible to study the distribution of species which can alter these nuclear relaxation parameters. We have utilized this aspect of MRI to study the distribution of manganese (II) ions in rat brain. Interest in evaluating this distribution is based on the neurotoxicity of Mn, which at excess levels can produce Parkinsonian type symptoms in humans. Magnetic resonance images of the brain of rats given various i.p. doses of manganese chloride showed localized time dependent changes due to the accumulation of manganese ions. The major increases in intensity of T1 weighted images were observed in the ventricles and in the pituitary and pineal glands. Since manganese frequently acts as calcium antagonist, such accumulations could lead to toxicological effects by antagonizing the action of calcium ions. The rapid appearance of manganese in the ventricular cerebrospinal fluid indicates that manganese readily crosses the filtration barrier of the choroid plexus. Although the large majority of MRI studies involve observation of protons, some studies have been carried out on other nuclei as well. During the past year we have carried out both spectroscopic and imaging studies on the distribution of cesium ions. The environment allows intra and extracellular resonances to be distinguished, as well as opening up the possibility for observing separate resonances for intracellular organelles.

1
AU - London RE
AU - Toney G
AU - Gabel SA
AU - Funk A
TI - Magnetic resonance imaging studies of the brains of anesthetized rats treated with manganese chloride
SI - CA/112/031830F/TOXLIT
SO - Brain Res. Bull.; VOL 23, ISS 3, 1989,229-35
AB - CBAC COPYRIGHT: CHEM ABS An understanding of the distribution

of manganese ions in the brain is of interest in connection with the development of an understanding of the neurotoxicity of this element. Information about the time-dependent biodistribution of manganese ions in the brains of intact rats subsequent to single i.p. injections of MnCl2 has been obtained from magnetic resonance imaging (MRI) studies. The enhanced MRI contrast is based on the redn. in the spin lattice relaxation time (T1) of water protons which exchange into the coordination sphere of the manganese ions. These studies indicate rapid and significant accumulations of water-accessible manganese in the ventricles, the pineal gland, and the pituitary gland. The rapid appearance of high levels of manganese in the ventricular cerebrospinal fluid indicates that manganese readily crosses the filtration barrier of the choroid plexus and is thereafter apparently absorbed by the ependymal surfaces of the ventricles and transported to the subarachnoid space.

2
AU - London RE
AU - Toney G
AU - Gabel SA
AU - Funk A
TI - Magnetic resonance imaging studies of the brains of anesthetized rats treated with manganese chloride.
AD - National Institute of Environmental Health Sciences, NIH, Res. Triangle Park, NC 27709.
UI - 90058144/MEDLINE
AB - An understanding of the distribution of manganese ions in the brain is of interest in connection with the development of an understanding of the neurotoxicity of this element. Information about the time dependent biodistribution of manganese ions in the brains of intact rats subsequent to single IP injections of MnCl2 has been obtained from magnetic resonance imaging (MRI) studies. The enhanced MRI contrast is based on the reduction in the spin lattice relaxation time (T1) of water protons which exchange into the coordination sphere of the manganese ions. These studies indicate rapid and significant accumulations of water accessible manganese in the ventricles, the pineal gland, and the pituitary gland. The rapid appearance of high levels of manganese in the ventricular cerebrospinal fluid indicates that manganese readily crosses the filtration barrier of the choroid plexus and is thereafter apparently absorbed by the ependymal surfaces of the ventricles and transported to the subarachnoid space.
SO - Brain Res Bull 1989 Sep;23(3):229-35

9
AU - Lyd:en A
AU - Larsson BS
AU - Lindquist NG
TI - Melanin affinity of manganese.
UI - 85043042/BACK83
AB - The melanin affinity of manganese was studied in vitro using

melanin isolated from beef eyes or human hair, and synthetic dopamine melanin, which is known to be structurally similar to the melanin present in the pigmented nerve cells in the human substantia nigra. In addition, the uptake of manganese in melanin containing tissues in vitro and in vivo was studied by whole body autoradiography. Manganese was bound to beef eye, human hair and synthetic dopamine melanin, and was taken up in pigmented tissues in mice and a monkey. Long-time exposure to manganese may cause a chronic extrapyramidal disorder. It is suggested that manganese, due to its neurotoxicity, may cause lesions in pigment containing neurones in the substantia nigra secondary to its accumulation on the neuromelanin.
SO - Acta Pharmacol Toxicol (Copenh) 1984 Aug;55(2):133-8

15
AU - Lyden A
AU - Larsson BS
AU - Lindquist NG
TI - Melanin affinity of manganese
SI - CA/101/124447Z/TOXLIT
SO - Acta Pharmacol. Toxicol.; VOL 55, ISS 2, 1984,133-8
AB - CBAC COPYRIGHT: CHEM ABS The melanin affinity of Mn was studied in vitro using melanin isolated from beef eyes or human hair, and synthetic dopamine melanin, which is structurally similar to the melanin present in the pigmented nerve cells in the human substantia nigra. In addn., the uptake of Mn in melanin contg. tissues in vitro and in vivo was studied by whole body autoradiog. Mn was bound to beef eye, human hair, and synthetic dopamine melanin, and taken up in pigmented tissues in mice and monkey. Long-time exposure to Mn may cause a chronic extrapyramidal disorder. Thus, Mn due to its neurotoxicity, may cause lesions in pigment contg. neurons in the substantia nigra secondary to its accumulation on the neuromelanin.

45
AU - LYDEN A
AU - LARSSON BS
AU - LINDQUIST NG
TI - Melanin affinity of manganese.
SI - HEEP/85/02550/TOXLINE
SO - ACTA PHARMACOL TOXICOL; 55 (2). 1984. 133-138.
AB - HEEP COPYRIGHT: BIOL ABS. The melanin affinity of Mn was studied in vitro using melanin isolated from beef eyes or human hair, and synthetic dopamine melanin, which is known to be structurally similar to the melanin present in the pigmented nerve cells in the human substantia nigra. The uptake of Mn in melanin containing tissues in vitro and in vivo was studied by whole body autoradiography. Mn was bound to beef eye, human hair and synthetic dopamine melanin, and was taken up in pigmented tissues in mice and a monkey. Long-term exposure to Mn may cause a chronic extrapyramidal disorder. Mn, due to its neurotoxicity, may cause lesions in pigment containing neurones in the

substantia nigra secondary to its accumulation on the neuromelanin. (These findings are related to the prevalence of chronic extrapyramidal symptoms in persons with extended occupational exposure to Mn.)

37
AU - Minter SG
TI - GROWING CONCERN OVER NEUROTOXINS
SI - HMTC/87/0005078/TOXLINE
SO - Occupational Hazards 49(2):35-38; 1987.
AB - HMTC Neurotoxic disorders are one of the 10 leading work-related diseases and are found in painters and in workers exposed to heavy metals (lead, mercury, manganese) and organophosphate pesticides. Symptoms of neurotoxicity include dizziness, nausea, numbness and tingling in hands and feet, loss of coordination, paralysis, personality and mood changes, reduced attention span, lack of alertness, and memory loss. Research, testing, and regulation in the area of neurotoxicity are discussed. New standards for levels of potential neurotoxins are suggested.

11
AU - Mohamed Ali M
AU - Murthy RC
AU - Mandal SK
AU - Chandra SV
TI - Effect of low protein diet on manganese neurotoxicity: III. Brain neurotransmitter levels
SI - CA/104/046821N/TOXLIT
SO - Neurobehav. Toxicol. Teratol.; VOL 7, ISS 5, 1985,427-31
AB - CBAC COPYRIGHT: CHEM ABS The effect of concurrent low protein (10% casein) diet and Mn exposure (3 mg/mL drinking water) on brain levels of dopamine (DA) [51-61-6], norepinephrine (NE) [51-41-2] and 5-HT [50-67-9] were investigated in F0-growing (90 days exposure), F0-diet rehabilitated (low.fwdarw.normal protein diet-28 days) and F1-weaned rats. Mn exposure in either diet group resulted in a significant increase in the DA and NE levels but a decrease in the 5-HT level. These effects were more pronounced in the rats fed the low protein diet, esp. in the F1-offsprings. Diet rehabilitation reduced the effects of Mn exposure.

22
AU - MORRIS CM
AU - CANDY JM
AU - COURT JA
AU - WHITFORD CA
AU - EDWARDSON JA
TI - THE ROLE OF TRANSFERRIN IN THE UPTAKE OF ALUMINUM AND MANGANESE BY THE IMR 32 NEUROBLASTOMA CELL LINE
SI - BIOSIS/87/36519/TOXLINE
SO - 621ST MEETING OF THE BIOCHEMICAL SOCIETY, LONDON, ENGLAND, UK, DECEMBER 17-19, 1986. BIOCHEM SOC TRANS; 15 (3). 1987. 498.

AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN NEUROBLASTOMA CELL LINE NEUROTOXICITY NEURODEGENERATIVE DISEASE

5
AU - Nachtman JP
AU - Delor S
AU - Brennan CE
TI - Manganese neurotoxicity: effects of varying oxygen tension and EDTA on dopamine auto-oxidation.
UI - 87259111/BACK83
AB - Manganese (Mn) is an essential trace element which, in excess, induces a chronic parkinsonian disease in animals and humans. Previous work indicated that Mn was more potent than other transition metal ions at stimulating dopamine (DA) auto-oxidation. We incubated Mn and DA at 37 degrees C and observed optical density changes at 480 nm, which is proportional to aminochrome formation. pO2 was held at O(N2), 160(O2), or 720 mm Hg(95%O2). Air without Mn produced approximately the same oxidation rate as Mn under N2; air plus Mn (33 uM) yielded a rate 5-fold greater than either air or Mn alone. Under elevated pO2, Mn (10 uM) produced approximately twice the rate seen with air. Addition of the chelating agent (EDTA, 1 mM) produced an 80% decrease in Mn-stimulated DA auto-oxidation. Results are consistent with a role for activated oxygen metabolites in DA depletion seen in chronic Mn intoxication.
SO - Neurotoxicology 1987 Summer;8(2):249-53

24
AU - NACHTMAN JP
AU - DELOR S
AU - BRENNAN CE
TI - MANGANESE NEUROTOXICITY EFFECTS OF VARYING OXYGEN TENSION AND EDTA ON DOPAMINE AUTO-OXIDATION
SI - BIOSIS/87/32239/TOXLINE
SO - NEUROTOXICOLOGY (LITTLE ROCK); 8 (2). 1987. 249-254.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM ANIMAL HUMAN PARKINSONIAN DISEASE

60
AU - Nachtman JP
AU - Tubben RE
AU - Commissaris RL
TI - Behavioral Effects of Chronic Manganese Administration in Rats: Locomotor Activity Studies
SI - NIOSH/00166953/TOXLINE
SO - Neurobehavioral Toxicology and Teratology, Vol. 8, No. 6, pages 711-715, 19 references, 19861986
AB - The effects of chronic administration of manganese (7439965) (Mn) on behavior in rats were tested using a measure of locomotor activity. Male Sprague-Dawley-rats were provided with drinking water containing 0 or 1mg/ml of manganese-chloride (7773015) (MnCl2). Mn did not affect body weights. After 14, 29, 41, and

65 weeks, the locomotor stimulant effects of administration of d-amphetamine (300629) were determined. Locomotor activity was increased in Mn treated rats at weeks five, six, and seven, but subsequently returning to control levels. Activity levels were higher in Mn treated animals. Mn treatment had no effect on habituation. By week 13 there was no Mn effect. d-Amphetamine significantly increased activity, and the observed interaction effect indicated greater stimulating effect of d-amphetamine in Mn treated animals. At weeks 41 and 65, there was no difference in the responsiveness of the two groups to the stimulant effects of d-amphetamine. The authors conclude that oral exposure of rats to a low dose of Mn resulted in a transient increase in both basal and d-amphetamine stimulated activity. These effects may represent an animal model for the "manganese madness" phase of Mn toxicity in humans.

9
AU - Nachtman JP
AU - Delor S
AU - Brennan CE
TI - Manganese neurotoxicity: effects of varying oxygen tension and EDTA on dopamine auto-oxidation
SI - CA/107/034596S/TOXLIT
SO - Neurotoxicology; VOL 8, ISS 2, 1987,249-53
AB - CBAC COPYRIGHT: CHEM ABS Incubation of Mn and dopamine (DA) at 37.degree. caused absorbance changes at 480 nm, which was proportional to aminochrome fermn. (formed during DA oxidn.). DA autoxidn. was approx. equal in the presence of air alone or Mn/N. DA with air and Mn together stimulated DA autoxidn. .apprx.5-fold over either air or Mn alone and 14-fold over control. Under elevated O, Mn produced .apprx.2-fold the rate as that with the air. EDTA addn. decreased Mn-stimulated DA autoxidn. by 80%. The results are consistent with the role of activated O metabolites in DA depletion seen in chronic Mn intoxication.

58
AU - Nachtman JP
AU - Delor S
AU - Brennan CE
TI - Manganese Neurotoxicity: Effects of Varying Oxygen Tension and EDTA on Dopamine Auto-Oxidation
SI - NIOSH/00169550/TOXLINE
SO - NeuroToxicology, Vol. 8, No. 2, pages 249-254, 15 references, 19871987
AB - The effects of oxygen (7782447) and manganese (7439965) on dopamine (51616) autooxidation were evaluated. Nitrogen, air, or a 95 percent oxygen/5 percent carbon-dioxide mixture was bubbled through 0.25 millimolar (mM) dopamine at 37 degrees-C in the presence or absence of 0.033 or 0.1mM manganese-chloride (7773015). In some experiments, 1mM EDTA was added. The effects on rate of dopamine autooxidation were evaluated by following the

rate of formation of aminochrome, a colored dopamine oxidation product, spectrophotometrically at wavelength 480 nanometers. The rate of autooxidation of dopamine in air without manganese was approximately the same as with manganese in the nitrogen atmosphere. The rate of autooxidation in air plus 0.033mM manganese was five times greater than in air or with manganese in nitrogen. In the hyperoxic atmosphere, 0.1mM manganese stimulated the rate of dopamine autooxidation further. Manganese had no stimulatory effect on dopamine autooxidation when EDTA was present. The authors conclude that these results support the notion that activated oxygen metabolites are involved in the dopamine depletion seen in chronic manganese intoxication.

2
AU - Oskarsson A
TI - Comparative effects of ten dithiocarbamate and thiuram compounds on tissue distribution and excretion of lead in rats.
AD - National Institute of Environmental Medicine, Stockholm, Sweden.
UI - 88004389/BACK86
AB - Combined treatment of rats with lead and disulfiram is known to cause increased levels of lead in brain and potentiation of the neurotoxicity of lead. Ten dithiocarbamate and thiuram compounds, including disulfiram, were compared for their efficacies in influencing tissue distribution of a trace dose of intravenously injected lead plus 203Pb in rats. The tested compounds were sodium diethyldithiocarbamate (DEDTC), sodium dimethyldithiocarbamate (DMDTC), tetraethylthiuram disulfide (disulfiram), a complex of zinc and manganese ethylenebisdithiocarbamate (mancozeb), manganese ethylenebisdithiocarbamate (maneb), sodium monomethyldithiocarbamate (metham), zinc propylene bisdithiocarbamate (propineb), tetramethylthiuram disulfide (thiram), zinc ethylenebisdithiocarbamate (zineb), and zinc dimethyldithiocarbamate (ziram). Pronounced effects on tissue distribution of lead were seen after peroral and subcutaneous administration of DEDTC, DMDTC, disulfiram, metham, thiram, and ziram. After peroral administration there was an increased uptake of lead in brain, liver, lung, and spleen and a decreased uptake in femur compared to control rats receiving only lead. Thiram was the most effective compound in enhancing lead uptake in brain, causing a 100-fold increase in 203Pb concentration at 72 hr survival. After subcutaneous administration, metham caused the highest increase in brain concentration of 203Pb. Fecal excretion of lead, which is the main excretory pathway, was decreased after peroral administration of disulfiram, ziram, and thiram to about 20% of the excretion in control rats at 48 hr. Urinary excretion of lead was significantly decreased in all the treated groups except the group treated with zineb. The effects on tissue distribution and excretion can be explained by in vivo formation of lipophilic complexes between lead and these compounds or their metabolites facilitating the transport of lead through cell membranes and the blood-brain barrier. Zineb, maneb, propineb,

and mancozeb did not cause similar effects on the tissue distribution of lead. The results of this study show that interactions can occur between lead and DEDTC, DMDTC, disulfiram, metham, thiram, and ziram, resulting in increased levels of lead in brain and probably potentiation of the neurotoxic effects of lead.
SO - Environ Res 1987 Oct;44(1):82-93

30
AU - PARATI EA
AU - PARENTI M
AU - CATTANEO C
AU - VESCOVI A
AU - CAPPELLETTI G
AU - SANTAGOSTINO A
TI - OXYGEN FREE-RADICAL INVOLVEMENT IN MANGANESE NEUROTOXICITY
SI - BIOSIS/86/36856/TOXLINE
SO - 16TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 1, WASHINGTON, D.C., USA, NOV. 9-14, 1986. SOC NEUROSCI ABSTR; 12 (1). 1986. 93.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT RAT

14
AU - PARENTI M
AU - RUSCONI L
AU - CAPPABIANCA V
AU - PARATI EA
AU - GROPPETTI A
TI - ROLE OF DOPAMINE IN MANGANESE NEUROTOXICITY
SI - BIOSIS/89/07107/TOXLINE
SO - BRAIN RES; 473 (2). 1988. 236-240.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN RAT ANTIOXIDANT TREATMENT VITAMIN E DOPAMINE CATABOLISM CELL CULTURE

39
AU - PARENTI M
AU - FLAUTO C
AU - PARATI E
AU - VESCOVI A
AU - GROPPETTI A
TI - Manganese neurotoxicity: Effects of L-dopa and pargyline treatments.
SI - BIOSIS/86/20594/TOXLINE
SO - BRAIN RES; 367 (1-2). 1986. 8-13.
AB - BIOSIS COPYRIGHT: BIOL ABS. Single, monolateral injection into rat substantia nigra of manganese chloride produced within two weeks from its administration a loss of dopamine in the striatum ipsilateral to the injected side. The effect was dose-dependent and was not extended to serotoninergic terminals present in this brain area, whose content in serotonin and 5-hydroxyindoleacetic acid was not affected. When L-DOPA + carbidopa or pargyline were given to these animals the decrease of striatal dopamine was more

marked. Moreover, rats treated two weeks before with a dose of manganese chloride that produced a 70-80% drop in striatal dopamine concentrations, rotated ipsilaterally to the dopamine-depleted striatum when injected with apomorphine, suggesting that in these animals the stimulatory effects of apomorphine were more relevant in striatum where presynaptic dopaminergic neurons were not affected by manganese chloride. These data indicate that the alterations of dopaminergic postsynaptic receptors may be different in parkinsonian and in manganese-intoxicated patients and that current therapy used for Parkinson's disease could be a hazard in treating manganese poisoning.

53
AU - Parenti M
AU - Rusconi L
AU - Cappabianca V
AU - Parati EA
AU - Groppetti A
TI - Role of Dopamine in Manganese Neurotoxicity
SI - NIOSH/00184240/TOXLINE
SO - Brain Research, Vol. 473, No. 2, pages 236-240, 32 references, 19881988
AB - The role of dopamine in manganese (7439965) neurotoxicity was studied in-vitro and in-vivo. Human fibroblasts were incubated with 0.25 millimolar (mM) manganese-chloride (7773015) in the presence or absence of 0.1mM dopamine, catalase, or superoxide-dismutase (SOD). The effects on cell viability were monitored by the trypan-blue dye exclusion test. Male Sprague-Dawley-rats were injected intraperitoneally with alpha-methyltyrosine (aMT), lisuride, or vitamin-E. They were injected intranigrally with manganese-chloride. The rats were killed 15 days later, and the brains were removed. The stria were dissected out and analyzed for dopamine. Similar experiments were conducted with 0.4 micromole nickel-chloride (7718549), 0.2 or 0.8 micromole magnesium-chloride (7786303), or 0.4 or 0.8 micromole lithium-chloride (7447418). In-vitro, dopamine significantly potentiated manganese induced cell killing. Catalase and SOD countered the effects of dopamine on manganese-chloride cytotoxicity. In-vivo, manganese significantly decreased striatal dopamine content on the side ipsolateral to the injection site, but not on the contralateral side. Lisuride, aMT, and vitamin-E countered the effect of manganese. Nickel-chloride, but not magnesium-chloride or lithium-chloride, decreased striatal dopamine concentrations on the side ipsolateral to the injection site. None of the compounds affected dopamine concentrations on the contralateral side. The authors conclude that their data support the notion that therapies for treating manganism and early stages of Parkinson's disease that increase dopamine availability may result in increased production of neurotoxic substances that can exacerbate the neuronal degeneration even though they may relieve

symptoms.

3
AU - Parenti M
AU - Rusconi L
AU - Cappabianca V
AU - Parati EA
AU - Groppetti A
TI - Role of dopamine in manganese neurotoxicity
SI - CA/110/052564W/TOXLIT
SO - Brain Res.; VOL 473, ISS 2, 1988,236-40
AB - CBAC COPYRIGHT: CHEM ABS MnCl2 increased cell mortality when added to human fibroblast cultures. The toxicity of the metal was greatly enhanced by dopamine; this effect was antagonized by the presence in the culture medium of catalase and superoxide dismutase enzymes. MnCl2 also caused a marked decrease of striatal dopamine concns. when infused into rat substantia nigra. Mn neurotoxicity was lowered by pretreating the animals with drugs that reduced striatal dopamine turnover rate. Administration of an antioxidant, such as vitamin E, also partially prevented striatal dopamine decline induced by intranigral Mn infusion. Therefore, the decreased availability or autoxidn. of dopamine attenuated Mn neurotoxicity. These findings are in agreement with previous observations suggesting that Mn increases toxic products originating from dopamine catabolism.

10
AU - Parenti M
AU - Flauto C
AU - Parati E
AU - Vescovi A
AU - Groppetti A
TI - Manganese neurotoxicity: effects of L-DOPA and pargyline treatments
SI - CA/104/181293G/TOXLIT
SO - Brain Res.; VOL 367, ISS 1-2, 1986,8-13
AB - CBAC COPYRIGHT: CHEM ABS Single, monolateral injection into rat substantia nigra of MnCl2 produced within 2 wk from its administration a loss of dopamine [51-61-6] in the striatum ipsilateral to the injected side. The effect was dose-dependent and was not extended to serotoninergic terminals present in this brain area. When L-DOPA [59-92-7] + carbidopa [28860-95-9] or pargyline [555-57-7] were given to these animals the decrease of striatal dopamine was more marked. Moreover, rats treated 2 wk before with a dose of MnCl2 that produced a 70-80% drop in striatal dopamine concns., rotated ipsilaterally to the dopamine-depleted striatum when injected with apomorphine, suggesting that in these animals the stimulatory effects of apomorphine were more relevant in striatum where presynaptic dopaminergic neurons were not affected by MnCl2. Thus, the alterations of dopaminergic postsynaptic receptors may be

different in parkinsonian and in Mn-intoxicated patients and current therapy used for Parkinson's disease could be a hazard in treating Mn poisoning.

5
AU - Pentschew A
AU - Ebner FF
AU - Kovatch RM
TI - Experimental Manganese Encephalopathy In Monkeys. A Preliminary Report
SI - NIOSH/00155798/TOXLINE65
SO - Journal of Neuropathology and Experimental Neurology, Vol. 22, No. 3, pages 488-499, 11 references, 19631963
AB - Neuropathological changes induced by manganese (7439965) were studied in monkeys. Five rhesus-monkeys were injected with repeated intramuscular doses of manganese-dioxide (1313139) suspended in olive oil. The animals were observed for clinical signs of toxicity. Nine to 24 months after the beginning of the study, the monkeys developed signs of neurotoxicity: excitability, clumsiness, and movements that resembled inebriation. One monkey was killed 14.5 months into the study and necropsied. This monkey had received two doses of manganese-dioxide, 2,000 and 3,500 milligrams, given 2 months apart. Pathological changes were found only in the brain. These involved proliferation of bizarre glial cells, loss of neurons in the subthalamic nucleus, and medial pallidum. Diffuse changes consisting of a ubiquitous metamorphosis to small and medium sized astrocytes were observed in about half of the glial population of the cerebrum, brain stem, and cerebellum. A single, asymmetrical, and circumscribed lesion characterized by small immature astrocytes with neuronal involvement was also observed. The authors note that the other monkeys are still being maintained under observation. The pathological changes in the brain of the necropsied monkey are virtually identical to those seen in human cases of manganese encephalopathy.

72
AU - Polakoff PL
TI - Warning: Nerve Poisons At Work
SI - NIOSH/00137619/TOXLINE
SO - Occupational Health and Safety, Vol. 51, No. 11, pages 15-18, 19821982
AB - Occupational hazards from exposure to neurotoxins are reviewed. Neurotoxins are known to cause nerve disorders resulting in confused, disoriented behavior. It was first observed among lead (7439921) and smelter laborers and later in workers exposed to methyl-n-butyl-ketone (591786). NIOSH lists over 150 chemicals in the American industry dangerous enough to require setting of Threshold Limit Values (TLV) of exposure. About 50 additional chemicals warrant TLVs because of secondary neurological and behavioral effects. The organic solvents identified as the largest group of neurotoxins include the aromatic coal-tar

(8007452) series and the aliphatic fatty petroleums. They enter the body chiefly by inhalation. Symptoms are ambiguous and often confused with psychological conditions. A typical symptom is tingling and numbness of hands and feet. Other symptoms develop slowly if exposure continues. Prolonged hospitalization or therapy is required. Irreversible damage to the central nervous system occurs in significant number of cases. Metals such as lead, mercury (7439976), and manganese (7439965) are also neurotoxic, affecting coordination, corticospinal tract dysfunction, and a variable degree of intellectual and emotional disorders. Besides the organic solvents and metals, carbon-monoxide (630080) (CO) is a large potential source of neurotoxicity because of the widespread combustion processes in industry. Even exposure to small concentrations of CO can result in mental dullness, memory loss, and depression. The author concludes that a greater commitment is required by the government to implement regulatory controls for neurotoxins in the workplace.

4
AU - Politis MJ
AU - Schaumburg HH
AU - Spencer PS
TI - Neurotoxicity Of Selected Chemicals
SI - NIOSH/00156967/TOXLINE65
SO - Experimental and Clinical Neurotoxicology, Spencer, P. S., and H. H. Schaumburg, Editors; Williams and Wilkins, London, pages 613-630, 127 references, 19801980
AB - The neurotoxicities of inorganic arsenic (7440382), barium (7440393), p-bromophenylacetylurea (30241862), carbon-tetrachloride (56235), cobalt (7440484), cuprizone (370810), cyanides, 2,4-dichlorophenoxyacetic-acid (94757), manganese (7439965), methanol (67561), methionine-sulfoximine (1982678), methylazoxymethanol-acetate (592621), methyl-bromide (74839), methyl-chloride (74873), organochlorine insecticides, paraquat (4685147), phenol (108952), polybrominated biphenyls, quinine (130950), styrene (100425), tetrachlorobiphenyl (26914330), toluene (108883), trichloroethylene (79016), and zinc (7440666) are discussed. The physical and chemical properties, uses, signs and symptoms of intoxication, experimental animal studies, and treatment protocols are given for each substance or class of compounds. A more thorough review of inorganic arsenic is given. Arsenic is ubiquitous and is present in minute amounts in all animals. Concentrations of 0.05 to 0.5 part per million are normally found in most human tissues. The predominant neurological complication of inorganic arsenic poisoning is peripheral neuropathy. Neuropathy may appear subacutely a few weeks after a massive overdose following an unsuccessful suicide attempt or epidemic of nutrient contamination. It may also develop insidiously after chronic, low exposure in industry. Chelation therapy is usually administered to individuals with arsenic neuropathy, but there is little evidence that treatment

of fully developed neuropathy has any effect on the course of the disorder.

40
AU - ROELS H
AU - SARHAN MJ
AU - HANOTIAU I
AU - DE FAYS M
AU - GENET P
AU - BERNARD A
AU - BUCHET JP
AU - LAUWERYS R
TI - PRECLINICAL TOXIC EFFECTS OF MANGANESE IN WORKERS FROM A MANGANESE SALTS AND MANGANESE OXIDES PRODUCING PLANT
SI - BIOSIS/85/10231/TOXLINE
SO - 2ND INTERNATIONAL SYMPOSIUM ON TRACE ELEMENTS, HUMAN HEALTH AND HAIR ANALYSIS, AMSTERDAM, NETHERLANDS, MAY 18-19, 1984. SCI TOTAL ENVIRON; 42 (1-2). 1985. 201-206.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN NEUROTOXICITY PULMONARY TOXICITY METAL TOXICITY DUST

21
AU - ROELS HA
AU - LAUWERYS RR
TI - PRECLINICAL TOXIC EFFECTS ON SOME FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM IN WORKERS MODERATELY EXPOSED TO MERCURY VAPOR OR MANGANESE DUST
SI - BIOSIS/88/12239/TOXLINE
SO - SYMPOSIUM ON TRACE ELEMENTS AND ENCEPHALOPATHY HELD AT THE 6TH SYMPOSIUM ON TRACE ELEMENTS IN MEDICINE, MUENSTER, WEST GERMANY, SEPTEMBER 25, 1987. TRACE ELEM MED; 4 (4). 1987. 180-181.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN NEUROTOXICITY

9
AU - Rudell B
AU - Kolmodin-Hedman B
AU - Hammarstrom U
AU - Wenngren B-I
AU - Nilsson-Granstrom A
TI - Dizziness and Oculomotor Dysfunction after Welding
SI - NIOSH/00191050/TOXLINE
SO - Journal of Aerosol Science, Vol. 19, No. 7, pages 1125-1128, 7 references, 1988
AB - The occurrence of dizziness and oculomotor dysfunction after welding was investigated, using a battery of oculomotor test. Seven welders having dizziness following welding and seven other welders not showing this symptom were subjected to a variety of oculomotor tests prior to and following 30 minutes of welding. Both groups of welders performed identical welding procedures with the same equipment under identical conditions. Both metal manual arc welding and metal inert gas welding were investigated. During the welding operations, particles were collected for

elemental analysis. Elemental analysis results showed that manganese (7439965) and iron (7439896) were present in all welding processes. Exposure to potassium (7440097), calcium (7440702), chromium (7440473), and nickel (7440020) were also possible, depending on the electrodes used. Oculomotor tests showed neurological disorders in four of seven welders with dizziness and for two of the welders without dizziness. Symptomatic welders exhibited impaired oculomotor function compared to the nonsymptomatic welders prior to any welding process. Oculomotor impairment subsequently increased for both groups following 30 minutes of welding. The authors suggest that manganese is neurotoxic and a possible cause for the neurological impairment.

48
AU - SCHEUHAMMER AM
TI - Chronic manganese exposure in rats: Histological changes in the pancreas.
SI - HEEP/84/09859/TOXLINE
SO - J TOXICOL ENVIRON HEALTH; 12 (2-3). 1983. 353-360.
AB - HEEP COPYRIGHT: BIOL ABS. Male Sprague-Dawley rats were treated i.p. for 30 days with 3.0 mg Mn/kg or an equal volume of 0.9% NaCl, then sacrificed by exsanguination through the aorta under pentobarbital anesthesia. The pancreas was removed immediately, fixed in 10% buffered formalin and processed for light microscopy. Significant pathological changes were observed in pancreatic tissue from Mn-exposed rats. These changes were characterized by a pancreatitis-like reaction consisting of expanded interacinar spaces, a thickened connective tissue capsule with invaginations of fibrotic connective tissue septa extending into the body of the gland, the presence of an inflammatory infiltrate of neutrophils, lymphocytes and macrophages and the separation of groups of acini from the body of the pancreas with occasional destruction of acinar cells. Since other peritoneal organs did not exhibit pathological changes, this study suggested that i.p. injected Mn2+ exerted a selective toxicity on pancreatic tissue and i.p. injection was not recommended as the route of administration of choice for chronic Mn neurotoxicity studies.

19
AU - Scheuhammer AM
TI - Chronic manganese exposure in rats: histological changes in the pancreas
SI - CA/100/046587H/TOXLIT
SO - J. Toxicol. Environ. Health; VOL 12, ISS 2-3, 1983,353-60
AB - CBAC COPYRIGHT: CHEM ABS Rats were treated i.p. for 30 days with either 3.0 mg Mn/kg or an equal vol. of 0.9% NaCl, then sacrificed by exsanguination through the aorta under pentobarbital anesthesia. Pathol. changes were obsd. in pancreatic tissue from Mn-exposed rats. These changes were characterized by a pancreatitis-like reaction consisting of

expanded interacinar spaces, a thickened connective tissue capsule with invaginations of fibrotic connective tissue septa extending into the body of the gland, the presence of an inflammatory infiltrate of neutrophils, lymphocytes, and macrophages, and the sepn. of groups of acini from the body of the pancreas with occasional destruction of acinar cells. Since other peritoneal organs did not exhibit pathol. changes, i.p. injected Mn2+ presumably exerts a selective toxicity on pancreatic tissue; therefore, i.p. injection is not recommended as the route of administration of choice for chronic Mn neurotoxicity studies.

1
AU - Segura-Aguilar J
AU - Lind C
TI - On the mechanism of the Mn3(+)-induced neurotoxicity of dopamine:prevention of quinone-derived oxygen toxicity by DT diaphorase and superoxide dismutase.
AD - Department of Biochemistry, University of Stockholm, Sweden.
UI - 90106700/MEDLINE
AB - Dopamine (DA) is rapidly oxidized by Mn3(+)-pyrophosphate to its cyclized o-quinone (cDAoQ), a reaction which can be prevented by NADH, reduced glutathione (GSH) or ascorbic acid. The oxidation of DA by Mn3+, which appears to be irreversible, results in a decrease in the level of DA, but not in a formation of reactive oxygen species, since oxygen is neither consumed nor required in this reaction. The formation of cDAoQ can initiate the generation of superoxide radicals (O2-.) by reduction-oxidation cycling, i.e. one-electron reduction of the quinone by various NADH- or NADPH-dependent flavoproteins to the semiquinone (QH.), which is readily reoxidized by O2 with the concomitant formation of O2-.. This mechanism is believed to underly the cytotoxicity of many quinones. Two-electron reduction of cDAoQ to the hydroquinone can be catalyzed by the flavoprotein DT diaphorase (NAD(P)H:quinone oxidoreductase). This enzyme efficiently maintains DA quinone in its fully reduced state, although some reoxidation of the hydroquinone (QH2) is observed (QH2 + O2----QH. + O2-. + H+; QH. + O2----Q + O2-.). In the presence of Mn3+, generated from Mn2+ by O2-. (Mn2+ + 2H+ + O2-.----Mn3+ + H2O2) formed during the autoxidation of DA hydroquinone, the rate of autoxidation is increased dramatically as is the formation of H2O2. Furthermore, cDAoQ is no longer fully reduced and the steady-state ratio between the hydroquinone and the quinone is dependent on the amount of DT diaphorase present. The generation of Mn3+ is inhibited by superoxide dismutase (SOD), which catalyzes the disproportionation of O2-. to H2O2 and O2. It is noteworthy that addition of SOD does not only result in a decrease in the amount of H2O2 formed during the regeneration of Mn3+, but, in fact, prevents H2O2 formation. Furthermore, in the presence of this enzyme the consumption of O2 is low, as is the oxidation of NADH, due to autoxidation of the hydroquinone, and the cyclized DA o-quinone is found to be fully reduced. These observations can be

explained by the newly-discovered role of SOD as a superoxide:semiquinone (QH.) oxidoreductase catalyzing the following reaction: O2-. + QH. + 2H+----QH2 + O2. Thus, the combination of DT diaphorase and SOD is an efficient system for maintaining cDAoQ in its fully reduced state, a prerequisite for detoxication of the quinone by conjugation with sulfate or glucuronic acid. In addition, only minute amounts of reactive oxygen species will be formed, i.e. by the generation of O2-., which through disproportionation to H2O2 and further reduction by ferrous ions can be converted to the hydroxyl radical (OH.). Absence or low levels of these enzymes may create an oxidative stress on the cell and thereby initiate events leading to cell death.

SO - Chem Biol Interact 1989;72(3):309-24

2

AU - SEGURA-AGUILAR J

AU - LIND C

TI - On the mechanism of the manganese-induced neurotoxicity of dopamine: Prevention of quinone-derived oxygen toxicity by DT diaphorase and superoxide dismutase.

SI - BIOSIS/90/09281/TOXLINE

SO - CHEM-BIOL INTERACT; 72 (3). 1989. 309-324.

AB - BIOSIS COPYRIGHT: BIOL ABS. Dopamine (DA) is rapidly oxidized by Mn3+-pyrophosphate to its cyclized o-quinone (cDAoQ), a reaction which can be prevented by NADH, reduced glutathione (GSH) or ascorbic acid. The oxidation of DA by Mn3+, which appears to be irreversible, results in a decrease in the level of DA, but not in a formation of reactive oxygen species, since oxygen is neither consumed nor required in this reaction. The formation of cDAoQ can initiate the generation of superoxide radicals (O2-) by reduction-oxidation cycling, i.e. one-electron reduction of the quinone by various NADH- or NADPH-dependent flavoproteins to the semiquinone (QH), which is readily reoxidized by O2 with the concomitant formation of O2-. This mechanism is believed to underly the cytotoxicity of many quinones. Two-electron reduction of cDAoQ to the hydroquinone can be catalyzed by the flavoprotein DT diaphorase (NAD(P)H:quinone oxidoreductase). This enzyme efficiently maintains DA quinone in its fully reduced state, although some reoxidation of the hydroquinone (QH2) is observed (QH2 + O2 - QH. + O2- + H+; QH. + O2 - Q + O2-). In the presence of Mn3+, generated from Mn2+ by O2- (Mn2+ + 2H+ + O2- - Mn3+ + H2O2) formed during the autoxidation of DA hydroquinone, the rate of autoxidation is increased dramatically as is the formation of H2O2. Furthermore, cDAoQ is no longer fully reduced and the steady-state ratio between the hydroquinone and the quinone is dependent on the amount of DT diaphorase present. The generation of Mn3+ is inhibited by superoxide dismutase (SOD), which catalyzes the disproportionation of O2- to H2O2 and O2. It is noteworthy that addition of SOD does not only result in an decrease in the amount of H2O2 formed during the regeneration of Mn3+, but, in fact,

prevents H2O2 formation. Furthermore, in the presence of this enzyme the consumption of O2 is low, as is the oxidation of NADH, due to autoxidation of the hydroquinone, and the cyclized DA o-quinone is found to be fully reduced. These observations can be explained by the newly-discovered role of SOD as a superoxide:semiquinone (QH) oxidoreductase catalyzing the following reaction: O2- + QH + 2H+ - QH2 + O2. Thus, the combination of DT diaphorase and SOD is an efficient system for maintaining cDAoQ in its fully reduced state, a prerequisite for detoxication of the quinone by conjugation with sulfate or glucuronic acid. In addition, only minute amounts of reactive oxygen species will be formed, i.e. by the generation of O2-, which through disproportionation to H2O2 and further reduction by ferrous ions can be converted to the hydroxyl radical (OH). Absence or low levels of these enzymes may create an oxidative stress on the cell and thereby initiate events leading to cell death.

69
AU - Seth PK
AU - Chandra SV
TI - Neurotransmitters And Neurotransmitter Receptors In Developing And Adult Rats During Manganese Poisoning
SI - NIOSH/00142523/TOXLINE
SO - NeuroToxicology, Vol. 5, No. 1, pages 67-76, 24 references, 19841984
AB - The effects of manganese (7439965) (Mn) on neurotransmitters and neuroreceptors in the adult and developing rodent are reviewed. Clinical, neuropathological, and biochemical evidence is presented to show that central nervous system dysfunction during Mn toxicity is due to disturbances in the neurotransmitter system. Effects of Mn on monoamine concentrations in the brain of experimental animals are summarized and alterations in the metabolism of the neurotransmitter relative to variations in species, dose, and mode of Mn exposure are noted. The high affinity binding of appropriate agonists and antagonists of the neurotransmitter is described. Data is presented to show the inability of the neonate to metabolize Mn, and the effect of Mn exposure on dopamine concentrations and receptor sensitivity are reviewed. Neonatal exposure to Mn produces a decrease in binding of spiroperidol to striatal membranes and of serotonin (50679) to frontal cortical membranes. Studies are described that suggest the involvement of dopaminergic, serotonergic, cholinergic, and gamma-aminobutyric-acid functions in Mn neurotoxicity. The dopaminergic system is more sensitive since the activity of this receptor is altered only at low doses of Mn. The mechanism by which the concentration of monoamines is altered after Mn exposure is discussed.

5
AU - Seth PK
AU - Chandra SV

TI - Neurotransmitters and neurotransmitter receptors in developing and adult rats during manganese poisoning.
UI - 84192183/BACK83
AB - Manganese neurotoxicity has been recognized among industrial workers as a consequence of chronic exposure to the metal in the form of fumes or dust. Hazards for the general population, including newborn and developing children, and other living organisms may also originate from prolonged low-level exposure to manganese and its organometallic compounds released into the environment as a result of their variety of applications. Experimental evidence has been presented to show that developing mice and rats are not able to excrete manganese for first 17-18 days of life, with excessive tissue accumulation, and their brain is more susceptible to the neurotoxic effects of manganese. Prolonged exposure to manganese causes depletion of dopamine and other monoamines in adult rats. The short-term exposure produces an increase in the binding of dopaminergic antagonist [3H]-spiroperidol to striatal membranes without affecting the other neurotransmitter receptors at low doses (10 mg/kg X 15). A higher dose (15 mg/kg X 15), causes a decrease in cerebral GABA, frontal cortical serotonin and striatal muscarinic binding and an increase in binding of [3H]-spiroperidol to striatal membranes. No significant changes occur in the levels of dopamine or serotonin at either of these two doses. The neonatal rat in certain respects shows a different effect on dopamine levels and receptor sensitivity. Exposure to manganese causes an increase in levels of dopamine and norepinephrine. Neonatal exposure to manganese (10 mg/kg X 15) produces a decrease in binding of [3H]-spiroperidol to striatal membranes and of serotonin to frontal cortical membranes.
SO - Neurotoxicology 1984 Spring;5(1):67-76

17
AU - Seth PK
AU - Chandra SV
TI - Neurotransmitters and neurotransmitter receptors in developing and adult rats during manganese poisoning
SI - CA/101/001868E/TOXLIT
SO - Neurotoxicology; VOL 5, ISS 1, 1984,67-76
AB - CBAC COPYRIGHT: CHEM ABS A review with 28 refs. on the neurotoxicity of Mn in developing and adult rat neurotransmitters and their receptors.

46
AU - SETH PK
AU - CHANDRA SV
TI - Neurotransmitters and neurotransmitter receptors in developing and adult rats during manganese poisoning.
SI - HEEP/84/12141/TOXLINE
SO - NEUROTOXICOLOGY (LITTLE ROCK); 5 (1). 1984. 67-76.
AB - HEEP COPYRIGHT: BIOL ABS. Mn neurotoxicity has been recognized among industrial workers as a consequence of chronic exposure to

Mn fumes or dust. Hazards for the general population, including newborn and developing children, and other living organisms, may also originate from prolonged low-level exposure to Mn and its organometallic compounds released into the environment as a result of their variety of applications. Experimental evidence was presented to show that developing mice and rats were not able to excrete Mn for the 1st 17-18 days of life, with excessive tissue accumulation, and their brain was more susceptible to the neurotoxic effects of Mn. Prolonged exposure to Mn caused depletion of dopamine and other monoamines in adult rats. Short-term exposure produced an increase in the binding of dopaminergic antagonist (3H)-spiroperidol to striatal membranes without affecting the other neurotransmitter receptors at low doses (10 mg/kg in cerebral GABA, frontal cortical serotonin and striatal muscarinic binding and an increase in binding of (3H)-spiroperidol to striatal membranes. No significant changes occurred in the levels of dopamine or serotonin at either dose. The neonatal rat showed a different effect on dopamine levels and receptor sensitivity. Exposure to Mn caused an increase in levels of dopamine and norepinephrine. Neonatal exposure to Mn (10 mg/kgroduced a decrease in binding of (3H)-spiroperidol to striatal membranes and of serotonin to frontal cortical membranes.

10
AU - Shukla GS
AU - Malhotra KM
AU - Chandra SV
TI - Effects of manganese on rat brain microsomal Mg2+-Na+-K+-ATPase: in vivo and in vitro studies.
UI - 84004303/BACK83
AB - The effect of manganese on brain microsomal Mg2+-Na+K+-ATPase was examined both in vitro and in vivo. Daily intraperitoneal administration of MnCl2 . 4H2O (Mn2+, 6 mg/kg) to the rats for a period of 90 days produced 10% (P less than 0.05) inhibition in the activity of Mg2+-ATPase, and 72 and 63% increases in the contents of manganese and copper, respectively, in the microsomal fraction of brain. In in vitro studies, lower concentrations of Mn2+ activated while higher concentrations inhibited the activity of brain microsomal ATPase. Addition of equal concentrations of Mn2+ + Cu2+ (8 mM) in vitro produced 8% inhibition in the activity of Mg2+-ATPase and 83% inhibition in Na+-K+-ATPase. Free Cu2+ ions were able to antagonize the effect of Mn2+ on ATPase in vitro and inhibited the activity of Mg2+-Na+-K+-ATPase with more pronounced effect of Na+-K+-ATPase. The lack of change in the activity of Na+-K+-ATPase in the brain microsomes of rats administered manganese, in spite of a significant increase in copper, could not be explained. It is, however, evident that a manganese-induced elevation in brain copper was not responsible for initiating biochemical changes in manganese neurotoxicity.
SO - Environ Res 1983 Oct;32(1):212-9

43
AU - SHUKLA GS
AU - SINGHAL RL
TI - THE PRESENT STATUS OF BIOLOGICAL EFFECTS OF TOXIC METALS IN THE ENVIRONMENT LEAD CADMIUM AND MANGANESE
SI - HEEP/85/05717/TOXLINE
SO - SYMPOSIUM ON TOXIC SUBSTANCES IN THE ENVIRONMENT, PART 2, KINGSTON, ONT., CAN., SEPT. 9-10, 1983. CAN J PHYSIOL PHARMACOL; 62 (8). 1984. 1015-1031.
AB - HEEP COPYRIGHT: BIOL ABS. RRM BEHAVIOR NEUROTOXICITY NEPHROTOXICITY GONADOTOXICITY METAL POLLUTION

20
AU - Shukla GS
AU - Malhotra KM
AU - Chandra SV
TI - Effects of manganese on rat brain microsomal magnesium-sodium-potassium ATPase: in vivo and in vitro studies
SI - CA/099/189228P/TOXLIT
SO - Environ. Res.; VOL 32, ISS 1, 1983,212-19
AB - CBAC COPYRIGHT: CHEM ABS Daily i.p. administration of MnCl2 (Mn2+, 6 mg/kg) to rats for a period of 90 days produced 10% inhibition in the activity of Mg2+-dependent ATPase, and 72 and 63% increases in the contents of Mn and Cu, resp., in the microsomal fraction of brain. In in vitro studies, lower concns. of Mn2+ activated whereas higher concns. inhibited the activity of brain microsomal ATPase [9000-83-3]. Addn. of equal concns. of Mn2+ + Cu2+ (8 mM) in vitro produced 8% inhibition in the activity of Mg2+-dependent ATPase and 83% inhibition in Na+-K+-dependent ATPase. Cu2+ ions were able to antagonize the effect of Mn2+ on ATPase in vitro and inhibited the activity of Mg2+-Na+-K+-dependent ATPase with more pronounced effect of Na+-K+ dependent ATPase. The lack of change in the activity of Na+-K+-dependent ATPase in the brain microsomes of rats administered Mn, in spite of a significant increase in Cu, could not be explained. It is, however, evident that a Mn-induced elevation in brain Cu was not responsible for initiating biochem. changes in Mn neurotoxicity.

70
AU - Shukla GS
AU - Malhotra KM
AU - Chandra SV
TI - Effects Of Manganese On Rat Brain Microsomal Mg2+-Na+-K+-ATPase: In Vivo And In Vitro Studies
SI - NIOSH/00141254/TOXLINE
SO - Environmental Research, Vol. 32, No. 1, pages 212-219, 23 references, 19831983
AB - The effects of manganese (7439965) alone or in combination with copper (7440508) on brain microsomal adenosine-triphosphate ATPase activities were studied in rats. Male ITRC-rats were intraperitoneally injected with 6 milligrams per kilogram

manganous-chloride (7773015) or with saline daily for 90 days. Brain microsomes were isolated and analyzed for manganese and copper content. ATPase activities stimulated by magnesium ion Mg ATPase or by sodium and potassium ions NaK-ATPase were assayed. Microsomal preparations from control brains were incubated with 2 to 10 micromolar concentration (microM) of divalent manganese, divalent copper, manganese and copper for 3 minutes, 0.1 to 10 millimolar concentration manganese for 3 minutes, or were untreated. Mg ATPase and NaK-ATPase activities were assayed. Compared to controls, in-vivo manganese treatment increased brain microsomal manganese and copper content 63 to 72 percent and decreased Mg ATPase activity. In in-vitro studies, Mg ATPase activity was increased 20 to 31 percent by 2 to 10microM manganese, decreased 10 to 15 percent by 4 to 10microM copper, and was only slightly affected by equimolar concentrations of manganese and copper. NaK-ATPase activity was increased 30 to 58 percent by 6 to 10microM manganese, decreased 46 percent by 2microM, decreased 83 to 94 percent by 4 to 10microM copper, and decreased 31 to 42 percent by 2 to 4microM each of manganese and of copper and 60 to 83 percent by 6 to 10microM each of manganese and copper. At higher manganese concentrations, both Mg ATPase and NaK-ATPase activities decreased in a linear fashion with increasing manganese concentrations. The authors conclude that manganese does not interfere with the inhibitory effects of copper on microsomal ATPase activities, and that a manganese induced increase in brain copper is not responsible for the observed neurotoxicity of manganese.

49
AU - SHUKLA GS
AU - MALHOTRA KM
AU - CHANDRA SV
TI - Effects of manganese on rat brain microsomal magnesium-sodium-potassium-ATPase: In vivo and in vitro studies.
SI - HEEP/84/04895/TOXLINE
SO - ENVIRON RES; 32 (1). 1983. 212-219.
AB - HEEP COPYRIGHT: BIOL ABS. The effect of Mg on brain microsomal Mg2+, Na+, K+-ATPase was examined in vitro and in vivo. Daily i.p. administration of MnCl2 4H2O (Mn2+, 6 mg/kg) to the rats for 90 days produced 10% ($P < 0.05$) inhibition in the activity of MG2+-ATPase, and 72 and 63% increases in the contents of Mn and Cu, respectively, in the microsomal fraction of brain. In in vitro studies, lower concentrations of Mn2+ activated while higher concentrations inhibited the activity of brain microsomal ATPase. Addition of equal concentrations of Mg2+-ATPase and 83% inhibition in Na+, K+-ATPase. Free Cu2+ ions were able to antagonize the effect of Mg2+ on ATPase in vitro and inhibited the activity of Mg2+, Na+, K+-ATPase with more pronounced effect of Na+, K+-ATPase. The lack of change in the activity of Na+, K+-ATPase in the brain microsomes of rats administered Mn, in spite of a significant increase in Cu, could not be explained. A Mn-induced elevation in brain Cu was not responsible for

initiating biochemical changes in Mn neurotoxicity.

42
AU - SILBERGELD EK
TI - MITOCHONDRIAL MECHANISMS OF LEAD NEUROTOXICITY
SI - HEEP/85/06693/TOXLINE
SO - NARAHASHI, T. (ED.). CELLULAR AND MOLECULAR NEUROTOXICOLOGY. MEETING, SAN DIEGO, CALIF., USA, AUG. 26-27, 1983. XV+304P. RAVEN PRESS: NEW YORK, N.Y., USA. ILLUS. ISBN 0-88167-028-6.; 0 (0). 1984. 153-164.
AB - HEEP COPYRIGHT: BIOL ABS. RRM HUMAN RAT DELTA AMINOLEVULINIC-ACID SYNTHASE ACETYLCHOLINE HEME SYNTHESIS MANGANESE COPPER ALUMINUM CADMIUM MERCURY

12
AU - SILVIUS JL
AU - PHILLIPS SJ
AU - WHEELER-USHER D
AU - FOX RA
TI - NEUROTOXICITY SECONDARY TO ORAL MANGANESE INGESTION A CASE REPORT
SI - BIOSIS/89/33585/TOXLINE
SO - ANNUAL MEETING OF THE SOCIETE CANADIENNE DE RECHERCHES CLINIQUES (CANADIAN SOCIETY FOR CLINICAL INVESTIGATION), EDMONTON, ALBERTA, CANADA, SEPTEMBER 22-25, 1989. CLIN INVEST MED; 12 (SUPPL. 4). 1989. B60.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT HUMAN OVER-THE-COUNTER HEALTH PREPARATIONS

1
AU - SLEPETIS RJ
AU - VIVEROS OH
AU - DANIELS AJ
TI - MANGANESE DEPLETES CATECHOLAMINES AND BIOPTERIN IN CULTURED BOVINE ADRENAL CHROMAFFIN CELLS
SI - BIOSIS/90/10261/TOXLINE
SO - 19TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PHOENIX, ARIZONA, USA, OCTOBER 29-NOVEMBER 3, 1989. SOC NEUROSCI ABSTR; 15 (2). 1989. 1312.
UI - 88120862/MEDLINE
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT NEUROTOXICITY

32
AU - SUTOO D
AU - AKIYAMA K
TI - THE EFFECT OF DIVALENT CATIONS ON THE BIOGENIC AMINE SYNTHESIS
SI - BIOSIS/86/33736/TOXLINE
SO - FOURTH INTERNATIONAL CONGRESS OF TOXICOLOGY, TOKYO, JAPAN, JULY 21-25, 1986. TOXICOL LETT (AMST); 31 (SUPPL.). 1986. 142.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM ABSTRACT MOUSE CALCIUM ZINC CADMIUM MERCURY MAGNESIUM MANGANESE DOPAMINE METAL TOXICITY NEUROTOXICITY

29
AU - TABACOVA S
TI - MATERNAL EXPOSURE TO ENVIRONMENTAL CHEMICALS
SI - BIOSIS/87/11196/TOXLINE
SO - SYMPOSIUM ON NEUROTOXICOLOGY IN THE FETUS AND CHILD HELD AT THE FOURTH INTERNATIONAL NEUROTOXICOLOGY CONFERENCE, LITTLE ROCK, ARK., USA, SEPT. 9-13, 1985. NEUROTOXICOLOGY (LITTLE ROCK); 7 (2). 1986. 421-440.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM HUMAN INFANT CHILD WORKER MANGANESE ARSENIC AROMATIC HYDROCARBONS CHLORINATED HYDROCARBONS HYDROGEN SULFIDE POLLUTION BEHAVIOR NEUROTOXICITY TERATOGEN

36
AU - VARNBO I
AU - PETERSON A
AU - WALUM E
TI - EFFECTS OF TOXIC CHEMICALS ON THE RESPIRATORY ACTIVITY OF CULTURED MOUSE NEUROBLASTOMA CELLS
SI - BIOSIS/86/06151/TOXLINE
SO - 3RD INTERNATIONAL WORKSHOP ON TISSUE CULTURE APPLICATION IN TOXICOLOGY, URBINO, ITALY, SEPT. 1984. XENOBIOTICA; 15 (8-9). 1985. 727-734.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM C-1300 CELL NEUROTOXICITY ETHANOL POTASSIUM CYANIDE METHANOL DMSO BENZIDINE PYRIDINE 2 5 HEXANEDIONE NICKEL ACETATE MANGANESE CHLORIDE PHENOL COBALT DICHLORIDE SODIUM SELENITE CADMIUM CHLORIDE POTASSIUM DICHROMATE SODIUM ARSENITE MERCUROUS CHLORIDE PENTACHLOROPHENOL HEXACHLOROPHENE METHYLMERCURY TRIETHYLTIN

10
AU - Vescovi A
AU - Gebbia M
AU - Cappelletti G
AU - Parati EA
AU - Santagostino A
TI - Interactions of Manganese with Human Brain Glutathione-S-transferas
SI - NIOSH/00190547/TOXLINE
SO - Toxicology, Vol. 57, No. 2, pages 183-191, 23 references, 1989
AB - The interactions of manganese-chloride (7773015) (MnCl2) with glutathione-S-transferase (GST) from the human brain were examined to investigate manganese (7439965) neurotoxicity. The interactions of GST with the known inducer of Parkinson like symptoms 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (28289545) (MPTP), and the MPTP metabolite 1-methyl-4-phenylpyridinium (MPP) were also studied for comparison. Frontal lobe tissue obtained during neurosurgery was homogenized and centrifuged to prepare the brain cytosol. GST activity was measured by spectrophotometry for glutathione (GSH) and 1-chloro-2,4-dinitrobenzene (CDNB) substrates. MnCl2 caused a dose dependent decrease in GST activity, which was reversible with increased incubation. GST activity in GSH substrate was

significantly diminished by manganese-chloride as was the Michaelis Menten affinity constant. Neither MPTP nor MPP had any effect on GST activity in either GHS or CDNB substrates. The authors conclude that neither MPTP nor MPP interact with human brain GST, and that manganese intoxication could result from both cytotoxic accumulation and a block of GST.

3
AU - Vescovi A
AU - Gebbia M
AU - Cappelletti G
AU - Parati EA
AU - Santagostino A
TI - Interactions of manganese with human brain glutathione-S-transferase.
AD - Lab. of Neuropharmacology, Neurological Institute C. Besta, Milan, Italy.
UI - 89318229/MEDLINE
AB - Chronic exposure to manganese-laden dusts induces, in humans and lower primates, neurological disorders with clinicopathological features that resemble idiopathic Parkinson's disease. As many authors have suggested, manganese neurotoxicity could be related to the capability of this metal to increase catechol autoxidation in catecholaminergic neurons, therefore increasing the formation of toxic compounds such as peroxides, superoxides, free radicals, and semi-orthoquinones. Oxidative stresses and consequent neuronal damage could then occur if physiological scavenger mechanisms fail in their detoxifying action. We here report that manganese chloride weakly inhibits, in a dose-dependent way by a reversible competitive mechanism, human brain glutathione-S-transferases possibly suggesting that manganese intoxication could cause intraneuronal accumulation of cytotoxic compounds. We also report that both 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a neurotoxin known to induce in man Parkinson-like syndromes, and one of its metabolites 1-methyl-4-phenylpyridinium failed to decrease glutathione-S-transferase activity.
SO - Toxicology 1989 Jul 17;57(2):183-91

13
AU - VESCOVI A
AU - GEBBIA M
AU - CAPPELLETTI G
AU - PARATI EA
AU - SANTIAGOSTINO A
TI - INTERACTIONS OF MANGANESE WITH HUMAN BRAIN GLUTATHIONE-S-TRANSFERASE
SI - BIOSIS/89/31048/TOXLINE
SO - TOXICOLOGY; 57 (2). 1989. 183-192.
AB - BIOSIS COPYRIGHT: BIOL ABS. RRM 1 METHYL-4-PHENYL-1 2 3 6-TETRAHYDROPYRIDINE PARKINSON'S DISEASE NEUROTOXICITY

5
AU - Vig PJS
AU - Nath R
AU - Desaiah D
TI - Metal Inhibition of Calmodulin Activity in Monkey Brain
SI - NIOSH/00192707/TOXLINE
SO - Journal of Applied Toxicology, Vol. 9, No. 5, pages 313-316, 23 references, 1989
AB - The effects of cations of vanadium (7440622) (Vd), cadmium (7440439) (Cd), mercury (7439976) (Hg), aluminum (7429905) (Al), lead (7439921) (Pb), and manganese (7439965) (Mn) on rhesus-monkey brain calmodulin activity were investigated. Samples of cerebral cortex were homogenized and calmodulin depleted synaptic plasma membranes were prepared. Brain fractions with endogenous calmodulin and calmodulin depleted fractions were incubated with various concentrations of aqueous solutions of the test metals for 5 minutes at 37 degrees-C. Calcium and magnesium ATPase and the magnesium ATPase activities were measured on the reaction mixtures to obtain the net calcium ATPase activity. No effect was noted on basal enzyme activity; however, each metal caused significant inhibition in calcium ATPase in brain fractions with calmodulin. Basal enzyme was affected by addition of exogenous calmodulin to to depleted fractions. Median inhibitory concentrations ranged from 3.0 micromoles Hg to 15.8 micromoles Vd; inhibition potency was observed to increase as follows: Hg, Cd, Pb, Mn, Al, Vd. The authors conclude that these toxic metal cations inhibit calmodulin activity in the primate brain.

2
AU - VINKEN PJ
AU - BRUYN GW
TI - Handbook of Clinical Neurology, Vol. 36. Intoxications of the nervous system, Part 1.
SI - HEEP/79/11699/TOXLINE65
SO - BOOK; 1979. 570.
AB - HEEP COPYRIGHT: BIOL ABS. This volume concentrates on metabolic disorders produced by exogenous toxins or metabolites. The 22 chapters cover the following topics: clinical aspects of lead poisoning, neuropathology of lead intoxication, biochemical aspects of lead neurotoxicity, manganese poisoning, bromide intoxication, methyl alcohol, and skeletal fluorosis. The text is supplemented by tables, micrographs, graphs, plates in both color and black-and-white, figures, chemical structures and subject index. Individual chapters are indexed in BIORESEARCH INDEX.

4
AU - Wang J-D
AU - Huang C-C
AU - Hwang Y-H
AU - Chiang J-R
AU - Lin J-M

AU - Chen J-S
TI - Manganese Induced Parkinsonism: An Outbreak due to an Unrepaired Ventilation Control System in a Ferromanganese Smelter
SI - NIOSH/00193140/TOXLINE
SO - British Journal of Industrial Medicine, Vol. 46, No. 12, pages 856-859, 21 references, 1989
AB - The etiology and prevalence of manganese (7439965) induced parkinsonism among workers at a smelting facility which had been in operation for 18 years was investigated. The facility consisted of three major departments: the ferromanganese smelting division, the foundry and the management office. The ventilation systems of the three furnaces of the smelting department were not in good working order during 1983. The old system was removed in December of 1984, but smelting operations were not discontinued during this period. Due to delays occurring in the installation process, workers were subsequently exposed to raised concentrations of manganese. Workers were divided into four groups, based on probable exposure levels. Each of the 132 workers underwent a comprehensive physical exam. A group of 123 was also interviewed for neurological symptoms. An area air sample taken about 3.5 meters from the top of the furnace, where the most exposed workers operated on the electrode, contained 28.8mg/m3 of manganese. Samples taken near the side of the furnace contained 1.0mg/m3. The air concentration of carbon-monoxide (630080) both near the side and near the top of the furnace was less than 15 to 60 parts per million. Six of the most highly exposed workers developed parkinsonism. No cases were found in the other workers. Furnace men were exposed to manganese concentrations of 0.5 to 1.5mg/m3 whereas foundry workers who worked in a separate building were exposed only to 0.1mg/m3. Blood manganese concentrations increased with exposure. The frequency of neurological symptoms and extrapyramidal signs increased with the degree of exposure to manganese and supported the possibility of some early stage cases of parkinsonism. No similar associations were found between the degree of exposure and the results of liver function tests, blood creatinine assays, electrocardiograms, and chest radiographs.

18
AU - WEISS B
TI - Manganese neurotoxicity (primates)
SI - CRISP/90/ES01247-130081/TOXLINE
SA - U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
SO - Crisp Data Base National Institutes Of Health

19
AU - WEISS B
TI - Manganese neurotoxicity (primates)
SI - CRISP/90/ES01247-140081/TOXLINE
SA - U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE;

NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
SO - Crisp Data Base National Institutes Of Health

17
AU - WEISS B
TI - Manganese neurotoxicity (primates)
SI - CRISP/90/ES01247-150081/TOXLINE
SA - U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INST. OF HEALTH, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
SO - Crisp Data Base National Institutes Of Health

61
AU - Yong VW
AU - Perry TL
AU - Godolphin WJ
AU - Jones KA
AU - Clavier RM
AU - Ito M
AU - Foulks JG
TI - Chronic Organic Manganese Administration in the Rat Does Not Damage Dopaminergic Nigrostriatal Neurons
SI - NIOSH/00166537/TOXLINE
SO - Neurotoxicology, Vol. 7, No. 1, pages 19-24, 20 references, 19861986
AB - The effect of long term administration of large amounts of organic manganese (7439965) on the dopaminergic nigrostriatal neurons of female Wistar-rats was investigated. Methylcyclopentadienyl-manganese-tricarbonyl (12108133) (MMT), dissolved in propylene-glycol, was injected subcutaneously in the rats every other day. Some rats received 24 injections, others 75 injections. Rats received 5mg/kg for the first dose, 10mg/kg for the second, 15mg/kg for the third, and 25mg/kg for the fourth, followed by 50mg/kg for each subsequent injection. Rats which survived the treatment had a mean body weight of 235 grams (g) at the end of 75 injections, compared with a mean of 234g for control animals. No behavioral differences were noted between control and MMT rats in open field and rotadrum testing. Manganese content in the cerebellum was more than twice the normal level immediately after the 24 injection procedure was completed. At one month's time, after 75 injections, the mean brain manganese content was only slightly higher than controls, indicating rapid clearance. No dysfunction of the nigrostriatal dopaminergic system was noted, either of a temporary or permanent nature. Histological studies of the zona compacta of the substantia nigra confirmed this conclusion. Comparable numbers of perikarya per unit area were found in both control and treated rats